

D2.2 Report of systematic review of published and unpublished data identifying important and relevant outcomes in AD and criteria for disease progression

116020 - ROADMAP WP2 – outcome definition

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Document history

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Definitions

- Partners of the ROADMAP Consortium are referred to herein according to the following codes:
 - **UOXF.** The Chancellor, Masters and Scholars of the University of Oxford (United Kingdom) – **Coordinator**
 - **NICE.** National Institute for Health and Care Excellence (United Kingdom)
 - **EMC.** Erasmus University Rotterdam (Netherlands)
 - **UM.** Universiteit Maastricht (Netherlands)
 - **SYNAPSE.** Synapse Research Management Partners (Spain)
 - **IDIAP JORDI GOL.** Fundació Institut Universitari per a la Recerca a l'Atenció Primària de Salut Jordi Gol i Gurina (Spain)
 - **UCPH.** Københavns Universitet (Denmark)
 - **AE.** Alzheimer Europe (Luxembourg)
 - **UEDIN.** University of Edinburgh (United Kingdom)
 - **UGOT.** Goeteborgs Universitet (Sweden)
 - **AU.** Aarhus Universitet (Denmark)
 - **LSE.** London School of Economics and Political Science (United Kingdom)
 - **CBG/MEB.** Aagentschap College ter Beoordeling van Geneesmiddelen (Netherlands)
 - **IXICO.** IXICO Technologies Ltd (United Kingdom)
 - **RUG.** Rijksuniversiteit Groningen (Netherlands)
 - **Novartis.** Novartis Pharma AG (Switzerland) – **Project Leader**
 - **Eli Lilly.** Eli Lilly and Company Ltd (United Kingdom)
 - **BIOGEN.** Biogen Idec Limited (United Kingdom)
 - **ROCHE.** F. Hoffmann-La Roche Ltd (Switzerland)
 - **JPNV.** Janssen Pharmaceutica NV (Belgium)
 - **GE.** GE Healthcare Ltd (United Kingdom)
 - **AC Immune.** AC Immune SA (Switzerland)
 - **TAKEDA.** Takeda Development Centre Europe Ltd (United Kingdom)
 - **HLU.** H. Lundbeck A/S (Denmark)
 - **LUMC.** Academisch Ziekenhuis Leiden – Leids Universitair Centrum (Netherlands)
 - **Memento.** CHU Bordeaux (France)
- **Grant Agreement.** The agreement signed between the beneficiaries and the IMI JU for the undertaking of the ROADMAP project (116020).
- **Project.** The sum of all activities carried out in the framework of the Grant Agreement.
- **Work plan.** Schedule of tasks, deliverables, efforts, dates and responsibilities corresponding to the work to be carried out, as specified in Annex I to the Grant Agreement.
- **Consortium.** The ROADMAP Consortium, comprising the above-mentioned legal entities.
- **Consortium Agreement.** Agreement concluded amongst ROADMAP participants for the implementation of the Grant Agreement. Such an agreement shall not affect the parties' obligations to the Community and/or to one another arising from the Grant Agreement.

Publishable summary

Alzheimer's disease (AD) is the commonest cause of dementia. It has an enormous global impact and cost which both continue to grow while disease modifying treatments are sought. Identifying the real world outcomes of AD that matter most to key stakeholders will help ensure that future treatments effectively improve the lives of those affected.

This systematic literature review (SLR) combined all available evidence on two questions.

1. Which outcomes of AD across the spectrum are prioritised by patients, carers and healthcare professionals?

The SLR found 34 studies carried out in eleven countries primarily using interviews, focus groups and surveys. The evidence described 32 outcomes of AD from the perspective of one or more of the stakeholder groups, which were grouped into seven overarching domains: cognition; functioning and dependency; behavioural and neuropsychiatric; length and quality of patient's life; caregiver-oriented; health, social care & treatment-related; and social issues.

The most commonly cited outcomes across the evidence base, from all stakeholders and from studies undertaken in multiple countries were memory or slowing of forgetfulness; activities of daily living; independence and patient autonomy; mental health; maintaining identity or personality; patient quality of life; caregiver burden and access to health services and disease information.

2. What do patients, carers and healthcare professionals consider to be a meaningful delay in progression of AD across the spectrum?

Limited evidence was found in three studies which reported that stakeholders wanted to slow memory decline, stabilise symptoms and maintain the patient's ability to undertake activities of daily living. However, quantification of the meaningfulness of such delays was not found. Two studies tested what constituted a meaningful change in the ADAS-Cog which is often considered a pivotal trial end-point. These highlighted differences in the applicability of measures at the individual and group level, again indicating a lack of robust and detailed evidence on what constitutes meaningful delay in progression of AD.

The SLR findings will be combined with evidence from WP2's stakeholder engagement work in order to produce a set of stakeholder-prioritised outcomes (Deliverable 2.3) and to support the rest of the ROADMAP programme.

1. Introduction

Alzheimer's disease (AD) is the commonest cause of dementia (Winblad et al., 2016; Scheltens et al., 2016). A typical presentation of AD is characterised by impairments to memory, executive functions and activities of daily living, with earlier-onset of the disease characterised by more atypical presentations like language or visual deficits (Scheltens et al., 2016). With disease progression come further deficits to memory, behavioural, neuropsychiatric and physical functions (Winblad et al., 2016), but the range and impact of symptomology or outcomes associated with AD across the spectrum is varied and diverse.

In the World Alzheimer Report, 2015, Prince et al. (2015) predicted that by 2050, 131 million people will be impacted by dementia worldwide and reported that the global cost of medical and social care was in excess of 487 billion US dollars in 2015. At the heart of these figures lie the patients, caregivers and healthcare professionals impacted by the disease each day at a personal level. Despite this global and personal impact, the root cause of the illness and effective treatments are still elusive (Posner et al., 2017; Scheltens et al., 2016).

Clinical trials involving people with AD continue to try and identify disease modifying treatments. While trials are designed to meet regulatory and registration requirements, there are concerns that they may not provide convincing evidence of direct relevance to patients, caregivers or healthcare professionals. There has been criticism that some clinical trials use inappropriate or inadequately sensitive endpoints (Cano et al., 2010; Posner et al., 2017; Rockwood et al., 2010) and it is unclear how much stakeholder input (other than that of regulators) is applied to clinical trial endpoint selection (Cano et al., 2010).

To illustrate, measures like the Alzheimer's Disease Assessment Scale-Cognitive (ADAS-Cog) are widely used during clinical trials (and often used as pivotal endpoints; Qaseem et al., 2008). Despite having high validity and reliability (Cano et al., 2010), research has demonstrated "ceiling" effects with this measure, whereby high percentages (often >75%) of AD diagnosed individuals perform well on large portions of the assessment, increasing the difficulty of detecting change, particularly in earlier disease stages (Cano et al., 2010; Raghavan et al., 2010; Snyder et al., 2014). Rockwood et al. (2010) also compared the ADAS-Cog with other clinical measures (goal attainment scaling (GAS) and a clinician's interview based impression of change (CIBIC)), demonstrating consistency in assessments only at the group level (i.e. at the group level, improvement to one measure showed improvement in the others) but not at the individual level (only 50% agreement across all measures). These factors outline the potential need to target outcome assessments based on the characteristics of the sample or indeed, the individual.

Further, discussion surrounding the use of clinical scales or patient reported outcome measures as endpoints is often critical. To illustrate, bodies like the U.S. Food and Drug Administration (FDA, 2009) outline an "endpoint model", whereby clinical trial endpoints are defined by success on predefined primary, secondary or exploratory endpoints (e.g., physiological measures or patient reported outcomes), stating that clinical trials *must succeed* on primary measures before attaining success on secondary measures. Black et al. (2009) outlined issues surrounding the use of primary and secondary measures during clinical trials, asking what happens when there is no improvement to, for example, a primary cognitive outcome measure, but improvement to secondary measures.

Additional discussion surrounds differences in the content of scales that measure the same outcome and the point at which these differences become redundant (Black et al., 2009; Delva et al., 2014; Harrison et al., 2016). This points to issues of heterogeneity across the research. Studies evaluating the relative success or applicability of outcome measures to AD across the spectrum have been critical of the heterogeneity of measures, the repeated and uncoordinated development of new measures and poor methodological quality of research studies relying on these outcome measures (Cano et al., 2010; Delva et al., 2014; Harrison et al., 2016; Posner et al., 2017). In addition to issues of measurement sensitivity and endpoint definitions discussed previously, this heterogeneity could hinder the detection of important changes during clinical trials.

Further limitations relate to AD patients' ability to report their symptoms, via impairments to concepts like self-awareness. Self-awareness relates to an individual's ability to recognise impairments (mentally or physically) in themselves, or *"the inherent ability that a person has to estimate his state in an accurate and objective manner"* (Fragkiadaki et al., 2016; Prigatano, 2010). Problems due to impairments in self-awareness when relying on patient report have been demonstrated even in the early stages of the disease, whereby patients with MCI overestimated performance on all cognitive domains, including general cognitive states, memory, visuospatial perception and executive functions in a study by Fragkiadaki and colleagues (2016). Therefore, to gain insight into the nature of the illness, effective communicative strategies could be applied in the clinical or research environment, and efforts made to accommodate challenges to communication with patients may help understand their real world experiences (Beuscher & Grando, 2009).

Understanding which real world AD outcomes are most relevant to crucial stakeholders, particularly patients, carers and healthcare professionals, may help guide future AD research towards the more robust development of relevant and effective treatments (Makady, 2017). Feedback on meaningful outcomes in both clinical trials and real world assessments to all stakeholders is essential and may facilitate streamlining or standardising of future AD related treatment goals.

The Australian Government and Alzheimer's Society (James Lind Alliance, UK) have conducted reviews to determine gaps in relation to current dementia research to guide future clinical and psychosocial research, stating that more work is required to understand the experiences of dementia patients and their caregivers (Alzheimer's Society, 2013; Seeher et al., 2010).

Although large amounts of potentially valuable real world data (which may be primarily related to symptomatic AD patients) are collected in healthcare settings, by insurance companies and other organisations, they are not well used in scientific research to support research and development.

In support of this goal, the international consortium "real world outcomes across the AD spectrum for better care" (ROADMAP) planned a group of systematic literature reviews of evidence of the prioritisation of AD outcomes and measures of disease progression, and what constitutes a meaningful delay in disease progression, from the perspective of key stakeholders. These reviews included evidence from three stakeholder groups (patients, carers and healthcare professionals) and covered the spectrum of AD. AD across the spectrum is interpreted as including all people affected by AD from subjective memory complaints and mild cognitive impairment (MCI), through preclinical and prodromal AD to confirmed AD dementia across disease severities.

2. Methods

The protocol for the combined reviews was registered with PROSPERO ([CRD42017075722](https://doi.org/10.1111/CRD4.17075722)). For ease of reference in the rest of this report, the combined reviews will be referred to as “the SLR”.

The SLR was conducted by members of the ROADMAP programme, co-ordinated by the Work Package 2 (WP2) co-lead Professor Cathie Sudlow and the University of Edinburgh team (UEDIN). Review tasks were led by UEDIN with support from WP2 partners at F. Hoffmann-La Roche Ltd (ROCHE), Alzheimer Europe (AE), Universities of Oxford (UOXF), Maastricht (UM), Copenhagen (UCPH) & Aarhus (AU), University Institute in Primary Care Research Jordi Gol (IDIAP JORDI GOL), GE Healthcare Ltd (GE), Takeda Development Centre Europe Ltd (TAKEDA) and Eli Lilly and Company Ltd (Eli Lilly). Individuals involved in each stage are listed in Annexe I.

While this work was being conducted, all contributors were employed by an academic, patient-focussed or commercial organisation which is a member of the ROADMAP consortium and therefore all have a professional interest in this topic. None of the SLR authors has additional conflicts of interest which would confer undue influence on their judgement on this topic.

2.1. Research questions

The SLR identified research studies which elicited information from stakeholders, answering one or both of the following research questions from their own perspective:

1. Which outcomes of AD across the spectrum are prioritised by patients, carers and healthcare professionals?
2. What do patients, carers and healthcare professionals consider to be a meaningful delay in progression of AD across the spectrum?

Evidence to answer the research questions was sought from a range of study types, including published primary or secondary research and unpublished “grey” literature. The primary research evidence base comprised studies which collected and reported quantitative, qualitative or mixed data based on research methods such as interviews, focus groups, surveys and Delphi or other consensus approaches. The potential secondary research base included systematic reviews of relevant primary research (i.e. studies gathering views of stakeholders). Reviews of measurement tools or diagnostic instruments used in AD were not included. Case studies, opinion pieces, commentaries and conference reports were not included. RCTs or other clinical trials which report on the outcomes of interventions for AD without eliciting stakeholder priorities were not included.

2.2. Population of interest

The focus of the SLR was AD across the spectrum. Studies involving only people whose dementia or cognitive impairment was suspected to be caused by a condition other than AD were excluded. As it was challenging to define what exactly is meant by AD across the spectrum and in order to avoid missing useful studies, this review aimed to include all people affected by AD including those in the pre-dementia stage (such as MCI) and those described by terms such as prodromal, pre-clinical or pre-symptomatic AD. These limits were set in an attempt to ensure the SLR could be delivered in

good time and would find a robust body of evidence on AD. This unfortunately excludes some people with important and relevant experiences in this area including people whose dementia was caused by a condition other than AD. Further, it is acknowledged that the search strategy would not find studies including people with AD unless they are defined as 'patients' or people with AD whose type of dementia was not specified. The implications of this were explored and are described in the limitations section of the discussion. Finally, it is important to note that people with MCI do not all go on to develop AD.

As the definition of AD has changed over time, with more recent studies likely to have a more consistent definition, studies published since 2008 were included in this review. In more recent definitions, AD is defined by a combination of a clinical and a biomarker diagnosis, but a clinical diagnosis was considered sufficient for the inclusion of studies in this review.

These pragmatic decisions were in consultation with expert advice within WP2 and were made in order to reach an achievable volume of articles to screen with the time and resources available by focussing the search process, thereby unavoidably limiting the scope of the review.

Each included study was required to provide evidence to answer one (or both) of the research questions from the perspective of one (or more) of the following groups:

1. People with AD across the spectrum;
2. People who care for individuals with AD across the spectrum informally, including but not limited to family members, unpaid caregivers and advocates;
3. Healthcare professionals or clinicians who look after people with AD across the spectrum, including but not limited to neurologists, geriatricians, psychiatrists, family doctors, nurses, therapists, professions allied to medicine, and formal, paid caregivers / support workers where results could be differentiated from informal, unpaid or familial caregivers.

2.3. Identifying the evidence

2.3.1. Searches

Relevant elements of existing search strategies developed by ROADMAP partners were brought together to achieve a consistent and comprehensive list of defining terms for condition, outcome, stakeholder and study types. Key studies identified by partners were examined using the [Yale MeSH analyser](#) to check for useful additional terms.

A search strategy for the Medline database was developed in collaboration with WP2 partners and expert advice at the UEDIN library to achieve a balance of sensitivity and specificity. This search is included in full in Annexe II. It is based on the combination of grouped terms indicated in Table 1 to retrieve evidence for each review question for each stakeholder group in distinct but internally consistent searches.

Table 1. Grouped search terms and the combination in which they were searched to retrieve evidence

	Research question 1 outcome priority	Research question 2 delay in disease progression
AD across the spectrum: includes terms from search strategy developed by AE & the Burden of Illness review (Kharawala, 2016)	✓	✓
Outcomes: keywords & MeSH terms based on the categories identified in WP2's "Universe of Outcomes" report (ROADMAP, 2017)	✓	
Priority: developed from terms in AE search strategy	✓	
Meaningful delay of disease progression: includes MeSH terms identified from key studies and related keywords		✓
Stakeholder group: patients & carers: developed from terms in AE search strategy	✓	✓
healthcare professionals: using MeSH and keyword terms		
Study method: developed from keywords in Roche and AE search strategies with relevant MeSH terms	✓	✓

The Medline search terms were translated for additional databases to maximise relevant citation retrieval for each stakeholder group. These are included in Annexe III.

- Patients & carers: PsycINFO (Ovid), CINAHL (EBSCO)
- Healthcare professionals (with European focus): Embase (Ovid)

As it was anticipated that studies relevant to a range of stakeholder groups would be identified in each of the databases, all citation lists were centrally collated and deduplicated before the first stage of screening. The combined results are summarised in Table 2, indicating the number removed by a two-stage deduplication process: firstly, automated deduplication during import to Endnote (matching on author, year, title and reference type) and secondly, manual screening, allowing for variations in author name such as use of initials or full names.

Table 2. Combined citation numbers retrieved

	Citations
Medline	1,705
Embase	3,616
Cinahl	1,755
PsycInfo	670
Initial total	7,746
Post deduplication	5,383
Limit to 2008-2017	3,772

Further relevant studies were gathered via expert recommendation and direct contact with authors of highly relevant conference abstracts identified in the searches. Relevant citations of key included studies were checked using Web of Science. Additionally, sources which may provide formal, but non-peer reviewed, evidence (grey literature) to answer the research questions, such as charity and patient organisation websites were searched. These include [Alzheimer Europe](#), [Alzheimer's Society](#), [James Lind Alliance](#) and [Alzheimer Scotland](#). Inclusion criteria and minimum quality thresholds consistent with other evidence were applied. The process for this grey literature search is included in Annexe IV.

2.3.2. Inclusion criteria

This sensitive search strategy was agreed through consultation within WP2 and review by the ROADMAP executive committee. Through further consultation and in-depth discussion of a selection of studies by a WP2 sub-group, a set of specific inclusion and exclusion criteria were established to identify a coherent, useful body of evidence to answer our research questions. These included all relevant studies which:

- Elicited information from an included stakeholder group who either have the condition or work with/care for someone who has the condition, which answered one or both of the research questions
- Used an appropriate and explicit research methodology
- Met a minimum quality threshold
- Were published between 2008 and 2017, inclusive.

2.3.3. Exclusion criteria

This SLR excluded research studies which:

- Did not allow information related to AD across the spectrum to be distinguished from other conditions such as stroke, multiple sclerosis and epilepsy, or other causes of dementia and cognitive impairment, unless they occurred as co-morbidities;
- Only included information on people with dementia or cognitive impairment caused by a condition other than AD, or dementia of an undefined or non-specific aetiology;
- Did not provide sufficient data to answer the research questions, such as commentaries and opinion pieces, conference abstracts or animal studies;
- Failed to provide the required information (year of publication, title, abstract) for filtering when extracted from source;
- Reported on AD outcomes as measured by diagnostic tools or interventions without including the views of one of our stakeholder groups on their relative importance.

2.3.4. Screening

On completion of searching and de-duplicating, 3,772 titles and abstracts were uploaded to [Covidence](#). Covidence is a screening and data extraction management system for systematic reviews. Members of the team then assessed each title and abstract for relevance to the research questions and to trigger acquisition of full text.

Due to the challenging timeline, half of titles and abstracts were assessed by a second team member and there was agreement in over 90% of decisions. This equated to a moderate Kappa statistic of 0.53 (due to the low number of included studies). Discrepancies between the two assessors were discussed with a third team member. On discussion of the conflicted decisions, the vast majority were found to be due to a desire by one of the two assessors to include a paper which was relevant to the programme in many ways but did not meet all the SLR inclusion criteria. Most often, study subjects had non-specific dementia or the paper was a scientific study of the outcomes of a particular intervention or treatment for AD without capturing the views of the stakeholders. There were no studies which required revision of the inclusion criteria. This suggested that disagreement resulted from a tendency to be oversensitive, with low risk of excluding relevant material. On this basis and with agreement from WP2, the team agreed to move forward to single screen for the remainder of the task.

2.3.5. Full-text appraisal

Each article which passed screening by title and abstract was reviewed in full text for relevance by two members of the team, with one or more others involved to resolve any discrepancies. Studies which provided evidence on one of our research questions were critically appraised using well-established, published tools from the [Critical Appraisal Skills Programme \(CASP\)](#) and [National Heart, Lung and Blood Institute \(NIH\)](#). An Excel spreadsheet was created for storing this information in standardised format.

Through consultation with WP2 colleagues and iterative discussions within the SLR working group, a minimum quality threshold was established, above which, studies were included in the review and full data extraction undertaken. Primarily, papers with no description of analysis, or poor / inconsistent

reporting of results throughout were excluded. In some cases, discussion related to the quality of the study in relation to the benefits of adding it to the review in terms of scope, via a “trade-off” process.

2.3.6. Data extraction and synthesis

A data extraction form was developed through consultation with WP2 partners and reference to existing work in similar projects. This form collated detailed information for each citation, including the research methodology, recruitment approaches, sample demographics (including stage of disease), findings, the approach to data analysis and synthesis, relevant quotes, and conclusions.

Thirty-four full text papers were passed forward for data extraction, references are included in Annexe VII.

The team member who undertook critical appraisal of full text articles completed its data extraction, with verification by a second member. In particular, the results section of each paper was carefully read and re-read, line-by-line, and relevant textual findings or quotes were extracted. Once an extraction form was completed for each paper, the findings and quotes were refined and compiled into a list. The ensuing secondary analysis adopted a form of narrative thematic synthesis. First, the quotes and findings were coded into general themes relating either to an outcome or an interpretation of meaningful delay of AD across the spectrum. Next, the themes with conceptual similarities were grouped together and an overarching category name was applied. This tentative framework of categories and respective themes was then presented to an expert panel of WP2 colleagues who provided feedback, which was then incorporated to provide a better fit of the data. It is important to note that many of the outcomes are multifaceted and may overlap across numerous categories. In such instances, the outcome was placed where it appeared to fit best according to clinical nosology (i.e. grouping behavioural, mental and neuropsychiatric outcomes together in accordance with the “international statistical classification of diseases and related health problems (ICD-10; World Health Organisation, 2017)) and previous WP2 activities (Deliverable 2.1).

In light of the largely inferential synthesis process and overlap in outcomes between categories, it is difficult to ascertain an explicit hierarchical structure of these outcomes in order of importance or priority. Nevertheless, the consistent appearance of outcomes discussed by the stakeholder groups was taken to infer their relative importance.

In addition to this SLR, further work within WP2 will inform the development of a prioritised list of outcomes. A quantitative survey will directly gather the priorities of patients, caregivers and healthcare professionals for AD or dementia with respect to outcomes of the disease. Further, in-depth group workshops have been designed to explore the views of stakeholders drawn from around Europe. Each workshop consists of a series of interactive consultation activities. The workshop activities aim to examine, in detail, the reasons why specific outcomes were / were not of importance.

In Annexe V, study characteristics tables outline the findings and whether priority or meaningful delay was inferred by the WP2 research group or explicitly stated by the participants in the study. Where necessary, these distinctions are stated when reporting results from the included studies.

2.4. Health economists

The list of stakeholders originally prioritised during the development of the protocol included health economists. A search comparable to the Medline search was developed for the Centre for Reviews and Dissemination ([CRD](#)) database and is included in Annexe III. Only two citations were retrieved, neither of which addressed the research questions.

It was agreed that a different approach to explore the perspectives of health economists would be appropriate, to include stakeholder engagement work and a pragmatic review of the literature around decision making by HTA organisations and regulatory bodies. This work is being undertaken separately by ROADMAP members at the London School of Economics (LSE). It will be used in combination with this SLR to establish the full list of stakeholder prioritised outcomes (Deliverable 2.3).

2.5. Grey literature

Searching for relevant evidence from grey literature sources was undertaken between 6th September and 1st November 2017 on the following sites:

- <http://www.greylit.org>
- <http://www.opengrey.eu>
- <http://explore.bl.uk>
- <http://www.alzscot.org>
- <https://www.google.co.uk>
- <https://www.alzheimers.org.uk>
- <http://www.alzheimer-europe.org/Research>
- <https://www.base-search.net/>
- <http://copac.jisc.ac.uk/search/form/main>
- <https://www.nice.org.uk/About/What-we-do/Evidence-Services/Evidence-Search>
- <https://scholar.google.com/>

Searches were performed using the keyword “Alzheimer” in combination with “outcome” or “progression”, applying date limits of 2008 to 2017 where possible. On sites where there was no search facility or a very basic one, manual screening of all available publications by title was undertaken. Further details are provided in Annexe IV.

If a search produced a list of websites, the first few paragraphs of each were screened in order to judge the suitability of the result for the research questions. Reports were screened based on the tables of contents, summaries and relevant sections. In accordance with the SLR exclusion criteria, PhD theses were not further screened. Published articles were not further screened but logged if they seemed relevant and were checked against the SLR’s peer-reviewed literature search results list. The first ten result pages of Google (which had several million hits for each search) were screened.

2.5.1. Evaluation of retrieved evidence

While some reports discussed the importance of involving patients and carers in decisions on meaningful and important outcomes, these were most often recommendations that did not translate

into direct actions with implications for the SLR research questions (Alzheimer's Disease Caregiving Advisory Board, 2009; Alzheimer's Society, 2012). One study had some concrete results, although the sample consisted of carers for people with dementia rather than AD specifically, and was published prior to the agreed threshold of 2008 (Alzheimer Europe, 2006).

For each of the results which appeared to be relevant at first screen but subsequently excluded, the reason for exclusion is provided in Table 9.

3. Results

3.1. Included evidence-base

Full text versions of all 126 studies which passed the screening phase were sought via the UEDIN library, inter-library loan, or direct contact with authors. All were retrieved. Ninety-two of the full text studies were excluded for failing to meet one or more of the inclusion criteria and 34 were included, see Figure 1.

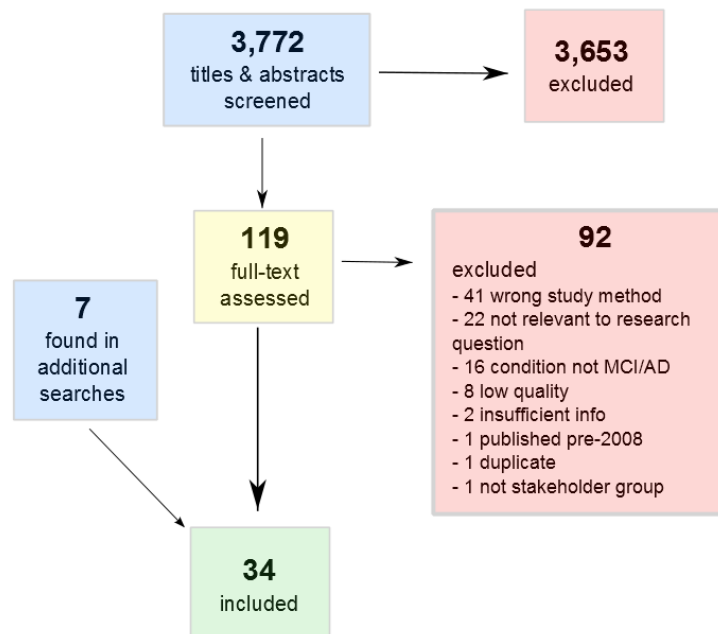


Figure 1. PRISMA flowchart showing citation numbers in each stage

3.1.1. Study characteristics

The included studies varied in methodological approach and quality. Here, the studies are appraised with regards to both the quality of fit within the current SLR and the overall methodological quality. Of the 34 included papers, 23 implemented a qualitative approach, nine utilised a quantitative approach, and two used a combination of these approaches in a mixed-methods design. Studies used a variety of methods of data collection, with several implementing more than one method of data collection: 18 studies employed interviews, eight studies used focus groups, six studies used surveys or questionnaires, one study used tape-recorded diaries, and three studies implemented another, bespoke approach. The number of included participants ranged from four to 1,116, with 20 studies recruiting patients, 23 studies recruiting caregivers and six which included the views of healthcare professionals. Only five studies included an explicit prioritisation of outcomes from the stakeholders. The remaining studies included relevant material which was used to infer the priority of outcomes from the stakeholders' perspective.

All studies were judged to have an appropriate research design to address the aims of the research. Twenty-four provided a detailed description of their recruitment strategy, with the remaining studies using a recruitment strategy which was not discernible from the paper. The majority of studies

confirmed ethical committee approval or equivalent had been obtained. Of those with a qualitative design, just six studies attempted to address the relationship between the researcher and the participants and the sources of bias which may derive from this relationship. Furthermore, of the studies with a qualitative analysis, 15 reported reaching data saturation and 19 discussed the credibility of their findings, including references to multiple analysts, triangulation or respondent validation. Annexe V lists the study characteristics in table format, Figure 2 shows the geographic locations where the studies were conducted and the number of papers which were obtained from each region.

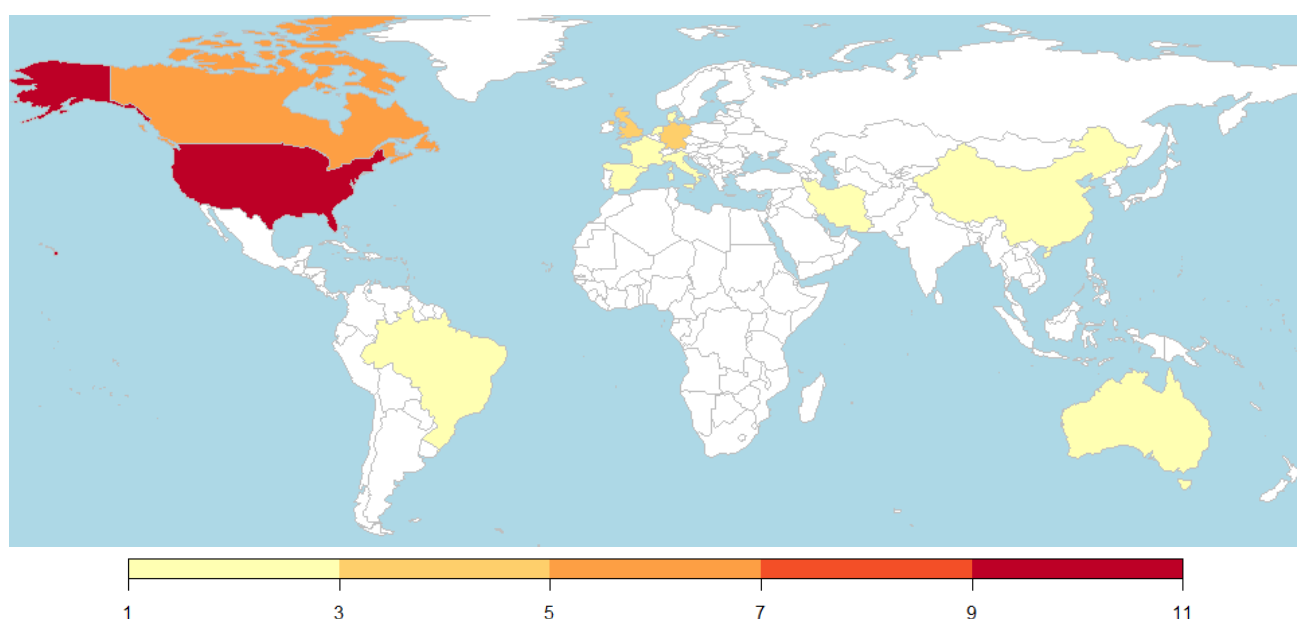


Figure 2. Countries in which the included studies were conducted (some studies included subjects from multiple countries)

3.2. Primary analysis: which outcomes of AD across the spectrum are prioritised by stakeholders?

Table 3 lists all outcomes which emerged from the evidence base listed alongside the stakeholder groups involved in each study who discussed the related outcome. Cohesive sets of outcomes which represent a particular domain of symptoms or experiences of AD across the spectrum were grouped together:

- Cognition;
- Functioning and dependency;
- Behavioural and neuropsychiatric;
- Social issues;
- Caregiver-oriented outcomes;
- Health / social care and treatment-related outcomes;
- Patient length and quality of life.

A greater variety of outcomes were identified for caregivers, whereas a narrower list of outcomes pertained to healthcare professionals. This is likely due to a smaller evidence base corresponding to healthcare professionals. Furthermore, a significant degree of overlap between the outcomes of patients and those of caregivers was observed, suggesting that patients and caregivers might share a similar perspective regarding the outcomes of greatest importance for AD across the spectrum. A number of outcomes were endorsed across all three stakeholder groups and within large illustrative samples – this consistency across patients, caregivers and healthcare professionals was taken to infer that these outcomes may be of high priority. This overlap is shown in Figure 3.

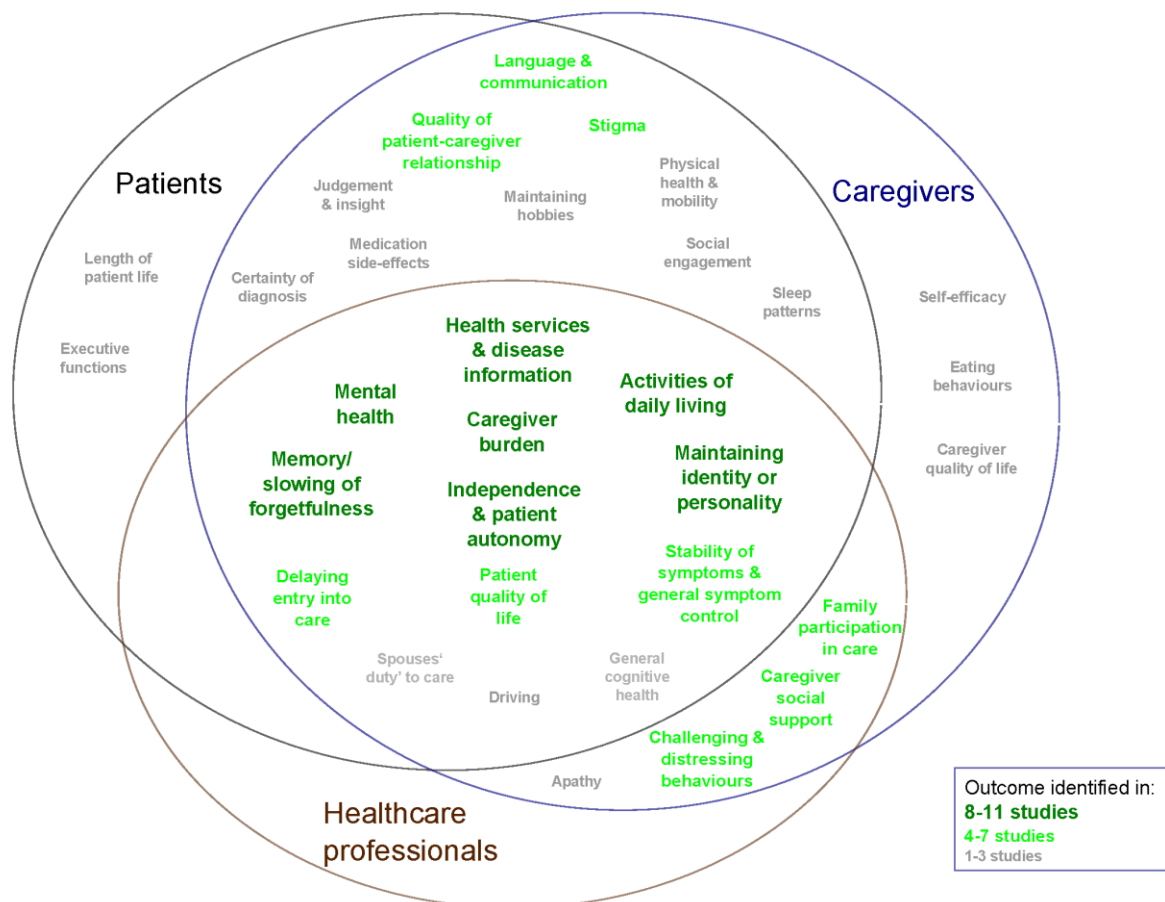


Figure 3. Venn diagram of the overlapping outcomes raised by patients, caregivers and healthcare professionals involved in the included studies

The following sections discuss the evidence for each outcome with links to supporting evidence from the source studies – either quotes (direct from the stakeholders) or findings.

As stated previously, the largely inferential synthesis process, overlap in outcomes between categories and heterogeneity among the included study base means it was difficult to ascertain an explicit hierarchical structure of these outcomes in order of importance or priority, and indeed, an outcome raised by one stakeholder group does not mean it is of little importance to the others. Therefore, it is key to acknowledge this methodological approach when reading this review. For more information, Annexe V reports the study characteristics of the evidence base and how importance of the included outcomes was determined for each study, either by inference by the SLR team or explicit reporting in the included papers.

Table 3. Priority outcomes with reference to stakeholder groups involved in studies who discussed the related outcome, their methodology and analytical approach, number of studies in which stakeholder groups were represented, the total number of studies and distinct countries from which evidence was drawn.

Outcomes of AD across the spectrum		Data collection methods used	Data analysis methods used	No. of articles in which stakeholder groups discussed the related outcome			No. of articles (range 1:11)	No. of countries (range 1:10)
				Patients	Caregivers	Healthcare profs		
Cognition	Memory / 'slowing of forgetfulness'	Focus groups, interviews, counselling sessions	Thematic & content analysis, grounded theory, survey data, analytic induction	5	6	1	10	6
	Language & communication	Focus groups, interviews, survey	Thematic & content analysis, IPA, survey data	3	3	-	6	3
	General cognitive health	Interviews	Analytic induction, grounded theory	1	1	1	2	2
	Judgement & insight	Focus groups	Grounded theory, survey data	2	1	-	2	1
	Executive functions	Focus groups, interviews	Grounded theory, survey data	2	-	-	2	2
Functioning & dependency	Activities of daily living	Focus groups, interviews, survey, diaries	Survey data, thematic & content analysis, analytic induction	3	7	2	10	7
	Driving	Focus groups, interviews	Content analysis, survey data	1	1	1	2	2
	Maintaining hobbies	Focus groups, interviews	Grounded theory, survey data, thematic analysis	3	1	-	3	3
	Eating behaviours	Survey, diaries	Survey data, thematic analysis	-	2	-	2	3
	Independence & patient autonomy	Focus groups, interviews	Grounded theory, thematic & content analysis, IPA	7	4	1	10	7
	Social engagement	Focus groups, interviews	Grounded theory, thematic analysis	2	1	-	3	3

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	Physical health & mobility	Focus groups, interviews	Grounded theory, thematic analysis	2	1	-	3	3
Behavioural & neuro-psychiatric	Mental health	Focus groups, interviews	Grounded theory, thematic & content analysis, survey data	3	5	1	10	6
	Maintaining identity or personality	Focus groups, interviews	Grounded theory, thematic, taxonomic & content analysis, grounded theory	4	4	1	9	7
	Challenging & distressing behaviours	Interviews, focus groups, survey	Survey data, thematic, content & taxonomic analysis	-	5	1	6	4
	Sleep patterns	Focus groups, interviews, counselling sessions	Survey data, thematic & content analysis	1	3	-	3	1
	Apathy	Focus groups, interviews	Quantitative, thematic analysis	-	2	1	3	2
	Self-efficacy	Interviews	Survey data	-	1	-	1	1
Patient quality and length of life	Patient quality of life	Interviews, surveys, diaries	Survey data, thematic analysis, analytic induction	2	3	1	6	7
	Length of patient life	Interviews	Thematic analysis	1	-	-	1	1
Caregiver-oriented	Caregiver burden	Focus groups, interviews	Survey data, content & taxonomic analysis	1	8	1	9	8
	Family participation in care	Interviews, counselling sessions	Content & thematic analysis	-	5	2	6	8
	Caregiver social support	Interviews, focus groups, survey, diaries	Thematic analysis, survey data	-	5	1	6	8
	Spouses' 'duty' to care	Interviews, diaries, counselling sessions	Thematic & content analysis	1	2	1	3	2
	Quality of patient-caregiver relationship	Interviews	Grounded theory, thematic analysis	2	2	-	4	3
	Caregiver quality of life	Survey	Survey data	-	2	-	2	6
Health / social care and treatment	Health services and disease information	Interviews, surveys, diaries, focus groups, counselling sessions	Content, thematic taxonomic analysis, grounded theory, survey data	5	8	2	11	10

related outcomes	Stability of symptoms and general symptom control	Interviews, focus groups, surveys	Survey data, thematic analysis, grounded theory, analytic induction	1	4	1	5	7
	Delaying entry into institutional care	Interviews, survey	Thematic analysis, survey data	1	1	2	4	3
	Medication side-effects	Surveys	Survey data	1	2	-	2	6
	Certainty of diagnosis	Focus groups, interviews	Content analysis	2	1	-	2	2
Social issues	Stigma	Interviews, diaries	Thematic & content analysis, grounded theory	1	3	-	4	3

Note: “IPA” = Interpretative phenomenological analysis, “no. of articles” = the total number of articles which discussed or reported the outcome (importance either inferred by researchers of the present review or ranked explicitly by the study’s participants), “no. of countries” = the total number of studies and distinct countries from which evidence was drawn, “no. of studies in which stakeholder groups represented” = the total number of articles where the outcome was raised by member(s) of the related stakeholder group.

3.2.1. Cognition

This category encompasses a variety of outcomes relating to cognitive functioning, including memory, language, judgement and insight, communication, and executive functions. Given the centrality of aberrant cognitive processes in the symptomatology of AD across the spectrum, it is unsurprising that cognition presented as a recurring outcome among patients, caregivers and healthcare professionals alike. The widest variety of cognitive concerns was reported by patients, with the most focused set reported by healthcare professionals.

3.2.1.1. Memory / “slowing of forgetfulness”

This outcome was informed by quantitative and qualitative data and covers concepts such as recalling names, events, dates, and general forgetfulness, alongside data which highlights the slowing of memory-loss as a key expectation of treatment. This outcome was discussed by all three stakeholder groups in different stages of the disease process (i.e. AD and MCI), suggesting memory may remain a central issue throughout the disease pathway. Furthermore, memory was discussed by stakeholders in Canada, USA, UK, Spain, Germany and Brazil, suggesting that this outcome may be important across the included cultures.

A range of qualitative research supported this finding. First, healthcare professionals and patients with early-AD reported improvement in memory as a key “expectation” of AD treatment (Andersen et al., 2008; *Quotes 1 and 15*). During interviews with patients with MCI, impaired recall recurred as a prominent theme (Dean et al., 2014a; *Finding 2*). Additionally, patients in various stages of the disease process also outlined the experience of impaired recall as “frustrating” or a “nuisance” when asked about their day-to-day experiences (Gordon et al., 2015; MacRae, 2008; 2010; *Quotes 3 and 4*).

Similarly, caregivers conveyed their frustration with having to manage patients’ pervasive memory problems and persistent questioning (Bronner et al, 2016; *Quotes 7 and 8*; Pavarini et al., 2008; *Quotes 12, 13 and 14*), sometimes leading to feelings of “desperation” amongst Latino caregivers (Gelman, 2010; *Quote 10*). Furthermore, during focus groups with caregivers of patients with MCI or early-AD, intact memory was perceived as a key factor of healthy ageing (Beard et al, 2009; *Quote 6*). Equally, this outcome was supported by quantitative findings. Of a sample of 25 patients with MCI, and their caregivers, 100% voiced concerns about patients’ memory or recall (Ropacki et al, 2017; *Finding 11*), demonstrating the importance of memory as an outcome of AD across the spectrum.

3.2.1.2. Language and communication

This outcome refers to cognitive aspects of verbal and written communication, such as verbal fluency and object naming. This outcome was largely elicited in the context of social difficulties, and was predominantly raised by patients with MCI or their caregivers.

Provoked by discussion in individual meetings and focus groups, patients with MCI reflected on how their deteriorating cognition had negatively impacted their ability to socialise (Gordon et al, 2015; *Quotes 20 and 21*). Relatedly, of a sample of 25 patients with MCI, 76% were specifically concerned about social interaction via communication (Ropacki et al, 2017; *Finding 22*). A spousal caregiver of

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a patient with MCI also reinforced this notion, and voiced feelings of “embarrassment” at their partner’s withdrawal in social situations as a result of deteriorating cognition (Lu & Haase, 2009; *Quote 24*). Moreover, following focus groups with nine spousal caregivers of patients with MCI, “communication issues” were explicitly identified as one of the four key areas to target in interventions for MCI (Lu & Haase, 2011; *Finding 23*), highlighting the importance of language and communication as an outcome in MCI in this sample. There was limited evidence of the importance of communication abilities further along the disease pathway.

Thirty-five familial caregivers of patients with AD identified “improvement to communication abilities” as the fourth most important outcome of AD, from a pre-determined list of 25 outcomes (Naumann et al, 2011; *Finding 25*).

With evidence derived from samples in the USA, UK and Germany, this outcome was most widely supported in Western countries: Language and communication are fundamental characteristics of human life and survival, regardless of geographical location, thus, this observation is likely due to an under-representation of non-Western countries in scientific literature.

3.2.1.3. General cognitive health

There was evidence across all three stakeholder groups discussing “general cognitive health”. This outcome encompasses general statements which infer the importance of cognitive functioning, without explicitly referring to a specific domain of cognition.

This was highlighted by patients and healthcare professionals in Canada who outlined an improvement in general cognition as a key “expectation” of treatment (Andersen et al, 2008; *Quotes 16 and 18*). Given that general cognition was highlighted as an expectation of treatment, the present researchers inferred this provided a strong indication of importance.

Further research pointed to the importance of general cognition, outlined during interviews with familial caregivers in China, who encouraged the patient to exercise and socialise with the hope that this would improve and preserve cognitive functioning (Dai et al, 2013; *Quote 17*).

3.2.1.4. Judgement and insight

These outcomes refer to the ability to retain an intuitive understanding of oneself, and of the disease process. The evidence in support of this outcome, albeit limited, was of particular relevance to individuals at an earlier stage of the disease process in the reviewed research.

Intact judgement and insight were identified as essential aspects of healthy ageing during focus groups with patients with MCI or early-AD (Beard et al, 2009; *Finding 29*). This outcome was also substantiated with quantitative evidence. Of a sample of 25 patients with MCI and their caregivers, 64% of patients and 60% of caregivers were concerned about patients’ insight into their problems (Ropacki et al, 2017; *Findings 30 and 31*), signifying the importance of this outcome within the study’s sample in the earlier stages of cognitive impairment.

3.2.1.5. Executive function

This outcome relates to patients’ ability to perform tasks requiring executive functioning, such as planning, multi-tasking and focussed concentration, and was raised by stakeholders in the Netherlands and the USA.

Particular concerns with executive functions were exclusively highlighted by patients with MCI. These concerns were elicited during discussion relating to professional duties, such as teaching or attending committee meetings (Gordon et al., 2015; *Quotes 26 and 27*). An MCI patient in Joosten-Weyn et al. (2008; *Quote 28*) also stated that issues with attentional control (concentration) were just as pressing as memory issues, which was inferred to indicate importance.

3.2.2. Functioning and dependency

This category encompasses outcomes relating to patients' ability to function independently and successfully in daily life. In particular, it refers to concepts such as physical health, mobility, activities of daily living, maintaining personal hobbies, social engagement, eating behaviours, driving, and patient autonomy. The outcomes within this category were most commonly discussed by patients and caregivers, with substantial overlap between the two stakeholder groups.

3.2.2.1. Activities of daily living

This outcome refers to the completion of daily activities in a functionally competent and independent manner. Instrumental activities of daily living encompass complex activities, such as cooking meals, housekeeping and managing finances, and are typically lost in the earlier stages of the disease process. Basic activities of daily living refer to simpler activities, such as using the toilet, eating meals, dressing oneself and self-hygiene. Deficits in these basic activities are typically observed much later in the disease process. A range of quantitative and qualitative evidence outlined this outcome among patients, caregivers and healthcare professionals at various stages across the AD spectrum.

For patients, there appeared to be some frustration at having to pass prior responsibilities of everyday life onto a spouse or family member (Frank et al, 2010; *Quote 36*). Of 25 patients with MCI, 52% voiced specific concerns about the impact of the disease on daily activities (Ropacki et al, 2017; *Finding 35*). Furthermore, when nine patients with MCI were asked what they considered to be key areas for interventions to target, they highlighted the self-management of activities (such as sorting medications, folding laundry, talking on the phone) as one of the four key areas, inferring priority of this outcome (Lu & Haase, 2011; *Finding 37*). In the reviewed studies, the evidence in support for activities of daily living as an important patient-reported outcome was primarily derived from those earlier in the disease process.

Similar, caregivers explicitly prioritised activities of daily living as a key outcome. However, caregivers of patients who were earlier in the disease process appeared to place more emphasis on instrumental activities of daily living as a key outcome, as opposed to basic activities of daily living.

From a selection of 12 predetermined outcomes, 33 caregivers of patients with MCI, on average, ranked "memory based activities of daily living" and "daily functioning" as the third and fifth most important MCI outcomes, respectively (Barrios et al, 2016; *Finding 38*). Nine caregivers outlined patients' self-management of daily activities (such as self-care, self-administering medications, meal preparation and household management) as a key outcome to be targeted in interventions for MCI (Lu & Haase, 2011; *Finding 41*). The daughter of a patient with MCI also expressed her pleasure at improvements in daily activities and displays of initiative from the patient, in a self-recorded diary in China (Cheng et al, 2016; *Finding 39*). Furthermore, of 25 caregivers of patients with MCI, 56% were specifically concerned about the patients' handling of money, and 68% about the patients' cooking (Ropacki et al, 2017; *Findings 42 and 43*). Therefore, there is a range of evidence supporting activities

of daily living as an important caregiver-reported outcome for those earlier in the disease process. However, in the reviewed studies, caregivers of patients who were further along the disease pathway appeared to shift their focus onto basic activities of daily living as an important outcome of AD across the spectrum, as opposed to instrumental activities of daily living.

Hauber et al. (2014) explicitly asked 803 caregivers of patients with AD to scale the importance of various functional outcomes from a predetermined list relating to daily activities, using the best-worst scaling method. Caregivers in the USA and Germany both agreed that “using the toilet without accidents” was the most important outcome, closely followed by “eating meals” (*Finding 40*). “Washing and drying the body completely” was regarded as the 3rd most important functional outcome in German samples, and the 5th most important in US samples (*Finding 40*). Similarly, during interviews with 14 familial caregivers in Brazil, showering was discussed as a particularly “difficult” and time-consuming activity by several caregivers (Lenardt et al, 2010; *Findings 44 and 45*). A further 14 interviews with familial caregivers in Brazil reinforced the notion that showering is “the hardest thing”, often resulting in agitation, violence and defiance from the patient (Pavarini et al, 2008; *Quotes 46, 47, 48, 49 and 50*). These caregivers also raised “using the toilet” and “getting dressed” as particularly problematic activities (*Quotes 51, 52, 53 and 54*). This range of evidential support indicates that basic activities of daily living are important from the perspective of caregivers at later stages along the disease pathway.

There is evidence to suggest that healthcare professionals acknowledge the importance of activities of daily living, however, there was little distinction between basic and instrumental activities of daily living. During interviews with healthcare professionals, improvements in daily activities were considered a key “expectation” of treatment (Andersen et al, 2008; *Quote 57*), and coping with daily life was considered the ‘most difficult’ aspect of the disease process (Bronner et al, 2016; *Quote 58*). Moreover, the outcome of activities of daily living was discussed across Canada, the USA, Brazil, the UK, Spain, Germany and China, thus spanning several continents and suggesting this outcome is important within the represented cultures.

3.2.2.2. Driving

Although issues with driving were often framed as an aspect of “independence and patient autonomy” and “activities of daily living”, it is considered separately here as it appeared as an issue to all stakeholders.

Following focus groups conducted in the USA with 25 patients with MCI and their caregivers, it emerged that 52% of patients and 64% of caregivers were concerned about patients’ “changes in driving” (Ropacki et al, 2017; *Findings 85 and 86*), with regards to safety as opposed to an indicator of disease progression.

Healthcare professionals in Germany also highlighted driving as a “big issue”, particularly for male patients, and it was typically discussed in light of associated legal considerations (Bronner et al, 2016; *Quotes 87 and 88*).

3.2.2.3. Maintaining hobbies

Patients and caregivers involved in research across the UK, USA and Denmark discussed the “maintenance of hobbies”. This outcome refers to patients’ continued ability to partake in preferred leisure activities and hobbies throughout the disease process.

For example, during interviews with 23 patients with MCI, the “impact of MCI on hobbies” emerged as a recurring theme (Dean et al, 2014a; *Quote 60*), inferring the importance of leisure time to patients in that sample. Furthermore, of 25 patients with MCI and their caregivers, 72% of caregivers and 80% of patients voiced specific concerns about leisure activities and hobbies. In addition, a patient with mild-AD expressed hope that they could continue with their hobbies throughout the disease process (Sorensen et al, 2008; *Quote 59*). Albeit based on a limited evidence base, these quotations and findings contribute towards the notion that the upkeep of hobbies is integral in maintaining the patients’ sense of self.

3.2.2.4. Eating behaviours

This relates to patients’ appetite or frequency of eating. This outcome was discussed by caregivers recruited to research in China, the USA and Germany. For example, the daughter of a patient with AD expressed her elation following an improvement in her mothers’ appetite, inferring the importance of this outcome to her (Cheng et al, 2016; *Quote 66*).

More explicitly, “eating meals” was ranked as the second most important outcome from a list of 10 functional activities by 803 caregivers of patients with AD, in Germany and the USA (Hauber et al, 2014; *Quote 67*).

3.2.2.5. Independence and patient autonomy

This outcome refers to the preservation of patients’ ability to function as an autonomous individual, both physically and psychologically, and was discussed by all stakeholder groups. Whilst independence is closely interrelated with functional capacity in the literature, autonomy refers to patients’ ability to self-govern. The concept of autonomy is also often associated with important decision-making processes, particularly with regards to legal, medical and social topics. Despite their differences, independence and autonomy are closely related, and the included literature reflects this. Thus, the two concepts were considered together under one outcome.

The strongest evidence was derived from interviews and focus groups with patients. For instance, a patient early in the disease process perceived the prospective loss of independence as “very negative” and defined healthy ageing as the ability to function independently (Beard et al, 2009; *Quote 68*). Other patients later in the disease process also explicitly discussed the importance of independence during one-to-one interviews (Hulko, 2009; *Quote 72*). The notion of patient autonomy was also expressed with regards to healthcare decisions and the inability to retain knowledge of the disease process, meaning important medical decisions may have to be shared with spouses and family members (Bronner et al, 2016; *Quote 69*). Several patients also conveyed annoyance or frustration at the prospect of being “controlled” or told what to do by spouses, children or even strangers (Frank et al, 2010; Joosten-Weyn et al, 2008; Malthouse & Fox, 2014; *Quotes 73, 71 and 75*). This incited discussion of the concept of spousal paternalism and the difficulties in accepting a major shift in relationship dynamics. In fact, nine patients with MCI suggested that future interventions should target communication with the spouse in order to promote patient autonomy, particularly with regards to telling the spouse “not to overprotect, not to take away their work too soon, and to allow the patient to do as much as independently as possible for as long as possible” (Lu & Haase, 2011; *Finding 74*). For those later in the disease process, autonomy was described in a pensive manner, with patients typically saddened by their loss of independence (Malthouse & Fox, 2014; *Quote 76*).

The importance of patient autonomy was also inferred through caregiver reports. Caregivers of patients with early-AD or MCI also identified “independent living” as a clear factor of healthy ageing (Beard et al, 2009; *Quote 77*).

In parallel with patients’ reported experiences of feeling “controlled” by their caregivers, caregivers expressed apprehension and difficulty in “taking over someone’s life” or “degrading” the patient (Lu & Haase, 2009; *Quotes 79 and 80*). It appeared clear that caregivers felt it important to encourage independence of the patient and to ensure they remained respected by society, both in the early and later stages of the disease process (Dai et al, 2013; *Quote 78*; MacRae 2008; 2010; *Quote 81*).

Healthcare professionals echoed similar sentiments. During an interview process, a variety of professionals discussed maintaining patient autonomy and the need to ensure the patient is not “patronised” (Bronner et al, 2016; *Quotes 82, 83 and 84*). Together, the literature points to “independence and autonomy” as an important outcome to all stakeholder groups at various stages of the disease process. Moreover, independence emerged from samples across Canada, the USA, Germany, Spain, Netherlands, the UK, and China, signifying that the ability to function autonomously in AD might be importance in the involved countries.

3.2.2.6. Social engagement

Evidence for the importance of “social engagement” was inferred from included studies which discussed socialisation and social support.

This was identified by patients and caregivers within studies conducted in the UK, USA and Brazil. A patient with MCI / early-AD outlined social support as a way to improve mood and encourage healthy ageing (Beard et al., 2009; *Quote 63*). Furthermore, following interviews with 23 patients with MCI, the “impact of MCI on social life” appeared as a recurring concept, suggesting this is of some importance to patients (Dean et al., 2014a; *Quote 64*). Finally, during interviews with 14 familial caregivers in Brazil, issues with social engagement were raised, with one caregiver remarking that the presence of people can make the patient feel “disturbed” and “afraid” (Pavarini et al, 2008; *Quote 65*).

3.2.2.7. Physical health and mobility

Evidence supporting this outcome came from patients and caregivers. This was informed by general statements relating to the importance of aspects of physical health, fitness and mobility in the disease process.

Focus groups conducted in the USA with 17 patients with MCI or mild-AD explicitly identified the notion of physical health as an important aspect of healthy ageing (Beard et al, 2009; *Quote 32*). Interviews conducted in the UK with 10 spousal caregivers of patients with AD also elicited subjective opinions of the importance of physical fitness in maintaining psychological well-being (Malthouse & Fox, 2014; *Quote 34*), suggesting that physical health is not only considered important as an individual entity, but is also thought to be crucial for maintaining other aspects of health during the disease process.

3.2.3. Behavioural and neuropsychiatric

This domain encompasses a range of outcomes relating to patients' psychological and psychiatric health and the associated behavioural issues, including apathy, self-efficacy, sleep patterns, mental health, challenging and distressing behaviours and the maintenance of patients' personality or identity. These outcomes were most commonly outlined by caregivers, presumably as behavioural and neuropsychiatric symptoms can often contribute substantially towards caregiver burden.

3.2.3.1. Mental health

This refers to changes in affect and irritation, as well as symptoms of anxiety, depression and reality distortion. These were reported across all three stakeholder groups. Furthermore, this outcome was highlighted by samples across Canada, USA, Netherlands, UK, Brazil and China, suggesting that it is a widespread concern in the represented geographic locations.

During focus groups with patients with MCI or early-AD, "good mental health" was identified as a prerequisite for healthy ageing (Beard et al, 2009; *Quote 97*). Similarly, throughout interviews with patients with MCI, "negative emotional reactions" recurred as a concern, particularly pertaining to feelings of irritation, anxiety, sadness and embarrassment (Dean et al, 2014a; *Finding 98*). Other patients with MCI noted feelings of sadness in the absence of any "obvious reason" (Joosten-Weyn et al, 2008; *Quote 99*). However, feelings of irritation were also prevalent. In a sample of 25 patients with MCI, 56% voiced concerns around the concept of "irritation" (Ropacki et al, 2017; *Finding 100*). Whilst the evidence in support of patient-reported importance of mental health exclusively related to the earlier stages of the disease, caregivers of patients in later stages also prioritised aspects of mental health.

Caregivers appeared particularly concerned about patients' emotional health and associated symptoms of depression or anxiety. When asked about the key areas which should be targeted in an intervention for MCI, caregivers believed that patient depression should be a top priority due to its prevalence in MCI (Lu & Haase, 2011; *Finding 103*). Thirty-three caregivers of patients with MCI also ranked "patient anxiety", on average, as the sixth most important outcome from a selection of 12 predefined outcomes (Barrios et al, 2016; *Finding 101*). During interviews, other spousal or familial caregivers pointed to the importance of mental health, and specifically encouraged the patient to engage in physical activity in order to improve mental wellbeing (Dai et al., 2013; Malthouse & Fox., 2014; *Quotes 102 and 104*). However, symptoms of reality distortion were only raised by caregivers of patients who were further along the disease spectrum. During interviews with 14 familial caregivers in Brazil, the issue of visual hallucinations was discussed as a source of great distress for patients (Pavarini et al, 2008; *Quotes 105 and 106*).

Similarly, interviews with healthcare professionals elicited discussion of mental health in AD (Bronner et al., 2016; *Quotes 107 and 108*). Professionals specifically highlighted depression as a major concern in AD, particularly in the period immediately following diagnosis. Overall, severe psychiatric symptoms, such as hallucinations, seemed to be discussed in relation to the later stages of the disease, whereas affective aspects of patients' mental health were predominantly discussed with regards to the earlier stages of the disease process – particularly during MCI. Perhaps the experience of adjusting to new limitations or accepting a serious diagnosis could serve as a risk period for poor affective mental health. However, it is important to acknowledge that the relationship between depression and AD across the spectrum is complicated. Many argue that depression could be a key

feature of prodromal AD (e.g. Sun et al., 2008) or that depression can serve as a risk factor for AD (Green et al., 2003; Herbert & Lucassen, 2016). Thus, despite the apparent importance of mental health in AD based on the reviewed evidence, the interpretation of this outcome as a primary measure necessitates further research to delineate this complex relationship.

3.2.3.2. Maintaining identity or personality

This outcome was informed by quantitative and qualitative evidence from patients, caregivers and healthcare professionals who outlined the relative importance of preserving key aspects of patients' sense of self, such as personality traits, knowledge or emotional bonds with others.

Patients with AD expressed fears of “losing themselves” or their mind as the disease progresses, partially fuelled by the stereotypical conceptualisation of AD as a “long, slow deterioration” (Joosten-Weyn et al., 2008; MacRae, 2008; 2010; *Quotes 118, 119 and 120*). Following interviews with 23 patients with MCI, the concept of “perceived change in personality” continually emerged as a prominent theme (Dean et al., 2014a; *Finding 117*). Another patient with mild-AD, seemingly saddened by his wife's change in behaviour towards him, explained his loss of identity in the context of the shifting dynamics in his closest relationship, claiming he is “no longer the man she married” (Sorensen et al., 2008; *Finding 121*).

Equally, caregivers discussed changes in patients' identity or personality, expressing feelings of loss for the person they once knew, or of hope to preserve any remaining identity traits. Again, this outcome appeared most among those with the closest relationship to the patient. During interviews with spousal caregivers, the wife of a patient with MCI expressed sorrow that her husband was “no longer the same person” (Lu & Haase, 2009; *Quote 122*). Similarly, during an interview with a daughter taking on a caregiving role for her mother with AD, the daughter prioritised the preservation of her mothers' personality as a “hugely important” outcome, even attributing the current perceived preservation as an effect of treatment (Smith et al., 2011; *Quote 123*). During interviews with familial caregivers, this notion of preserving identity was reinforced, with one caregiver remarking that it is “difficult to face the fact that someone like her is now like this”, referring to the patient's previous role as a Portuguese teacher (Lenardt et al., 2010; *Quote 124*). Furthermore, of a sample of 25 caregivers of patients with MCI, 80% outlined concerns about patients' personality during focus groups (Ropacki et al, 2017; *Finding 125*). Finally, a healthcare professional, interviewed in Germany, highlighted the “longing” that patients and caregivers display to preserve patients' identity as long as possible (Bronner et al, 2016; *Quote 126*).

Ultimately, this outcome is endorsed by stakeholders at various points along the disease process and situated in a variety of countries, such as Canada, USA, Brazil, Netherlands, Germany, Denmark, and the UK, inferring that the preservation of patients' identity is considered an important outcome across the included countries.

3.2.3.3. Challenging and distressing behaviours

This encompasses patient behaviours such as verbal or physical aggression, anger, and injurious behaviours and was identified by caregivers and healthcare professionals in the USA, Germany, Brazil and Iran.

A spousal caregiver of a patient with MCI spoke of their own “unethical” behaviour to attempt to pre-empt and avoid patients' difficult or challenging behaviours (Lu & Haase, 2009; *Finding 109*). During

interviews with 14 familial caregivers, the concept of challenging behaviours was reiterated, with one caregiver describing the patient's behaviour as "worse than a child" (Lenardt et al, 2010; *Quote 112*). Similarly, during an additional 14 interviews with familial caregivers, agitation was discussed as a source of challenging and "horrible" behaviour (Pavarini et al, 2008; *Quote 113*). Furthermore, a sample of 35 familial caregivers ranked "improvement in behavioural symptoms" as the ninth most important outcome of AD, of a selection of 25 predetermined outcomes (Naumann et al, 2011; *Finding 110*). Additionally, of a sample of 25 caregivers of patients with MCI, 64% voiced specific concerns regarding patients' "frustration" (Ropacki et al, 2017; *Finding 111*).

Interestingly, of all the included samples, a sample of formal caregivers in Iran appeared to apply more importance to challenging behaviours as a priority outcome. The formal caregivers outlined "bad-temper", "swearing", "yelling" and "aggression" as key challenges to providing care (Yektatalab et al, 2013; *Quotes 114, 115 and 116*). Perhaps this outcome was of greater relevance to this subgroup due to the lack of a personal duty to the patient which is typically observed in alternative, informal caregiving dyads. Nevertheless, challenging and distressing behaviours can have a significant impact on caregiver burden and quality of life. Thus, it is unsurprising that this outcome was predominantly endorsed by those in a direct caregiving role.

3.2.3.4. Sleep patterns

This outcome refers to sleep patterns or the duration or frequency of sleep. It was predominantly highlighted by caregivers in the USA, though patients also voiced concerns.

Of a sample of 25 patients with MCI and their caregivers, 56% of patients and 64% of caregivers stressed concerns regarding patients' sleep (Ropacki et al, 2017; *Finding 93*). Furthermore, during counselling sessions with Latino familial AD caregivers, sleep was raised as a recurring issue, with negative effects on the caregivers themselves (Gelman, 2010; *Quote 95*). Similarly, a familial caregiver of a patient with MCI spoke of frustrations deriving from the patients' "backwards" sleeping patterns (Blieszner & Roberto, 2010; *Quote 94*). Sleep patterns were raised by caregivers and patients in several stages of the disease process, but it is important to note that the caregivers who raised this issue were largely familial caregivers in the reviewed papers. It might be that dysfunctions in sleep cause greater burden for familial or live-in carers, and as such, this outcome may be of greater importance to this subgroup of stakeholders.

3.2.3.5. Apathy

This relates to the patient retaining a general engagement with their environment and an interest, motivation or enthusiasm for everyday life. This outcome was discussed by caregivers and healthcare professionals, and was highlighted in samples derived from the USA.

A spousal caregiver of a patient with MCI voiced frustration at her husbands' lack of motivation in the household, thereby increasing her own burden of household duties (Blieszner & Roberto, 2010; *Quote 89*). Ropacki et al (2017) also reported that of a sample of 25 caregivers of patients with MCI, 60% were concerned about patients' lack of "interest or motivation" (*Finding 90*). Healthcare professionals recruited to interviews also outlined a key "expectation" of treatment would be to increase patients' general engagement with the environment (Andersen et al, 2008; *Finding 91*), thereby targeting apathy.

3.2.3.6. Self-efficacy

“Self-efficacy” refers to patients’ belief and confidence in their abilities. There was evidence of prioritisation of this outcome by caregivers in the USA (Barrios et al, 2016).

Thirty-three caregivers of patients with MCI ranked this outcome second most important on average out of a selection of 12 predetermined outcomes (Barrios et al, 2016; *Finding 92*). However, this limited evidence base makes it difficult to ascertain the relative importance of this outcome with confidence.

3.2.4. *Patient quality and length of life*

Patient quality of life was a recurring theme throughout the literature. Evidence supporting the importance of this outcome came from statements pertaining to enjoying a fulfilling life and living with dignity, in addition to explicitly ranking quality of life as a priority outcome, or outlining its importance in surveys. Similar, AD patients also outlined the importance of living a long life. Hence, these outcomes were grouped together given the relationship between quality of life and longevity, which are the core of the concept of quality adjusted life years (QALY; Weinstein et al., 2009).

3.2.4.1. Patient quality of life

This outcome was outlined by patients, caregivers and healthcare professionals. Data came from semi-structured interviews, surveys and tape-recorded diaries, with samples from the USA, Brazil, Canada, France, Germany, Spain and China, signifying representation across North/South America, Europe and Asia, signifying generalisability across the included cultures. Priority was inferred from qualitative interviews and explicit rankings, which pointed to high importance.

MacRae (2008; 2010) produced two papers involving nine AD patients using semi-structured interviews. Participants outlined their desire to enjoy “every minute” of their lives until their illness took over, stating that they did not want to think of the future, but would rather lead a fulfilling life while they can, and that they would not “trade [their lives] with anyone” (*Quotes 228, 229 and 230*). In accordance, survey data from 502 AD patients in Kurz et al. (2008) reported that 90% of participants voted having “the best possible quality of life” and “having the ability to enjoy life” as the two outcomes with the “greatest importance” amongst those reported in the study, alongside “treatment that helps control symptoms”, and “feeling safe at home” (*Finding 231*).

Further, an AD caregiver from the 57 tape-recorded diaries of Cheng et al. (2016) noted that she wanted to increase her efforts to improve her mother’s quality of life (*Quote 233*). This finding is supported by the 33 MCI caregivers in Barrios et al. (2016), who ranked patient quality of life as the most important outcome from a predetermined list of 12, ranked over all other caregiver- and patient-related outcomes (*Finding 232*). Further evidence is provided from the 35 AD caregivers of Naumann et al. (2011), who ranked 25 outcomes for importance (*Finding 234*), voting “extension of a dignified life” as the outcome with top priority: Although this outcome does not explicitly mention “quality of life”, one can infer that living a dignified life relates to living a life of worth, inferred to relate to quality of life. Thus, the relevance of this outcome is based on two caregiver samples and a large AD patient sample ranking patient quality of life as the outcome with greatest importance.

A healthcare professional from the 11 semi-structured interviews in Andersen et al. (2008) outlined patient quality of life as a key “expectation” of treatment, indicating it is a main target for treatment

(Quote 235). Given that clinicians prescribe medications with the hope that they will improve patient quality of life, one can infer the outcome's importance to the healthcare professional group.

3.2.4.2. Length of patient life

A small body of evidence from AD patients in Canada discussed living a long life, relating to longevity and staying healthy for as long as possible.

The nine AD patients in MacRae (2008; 2010) stated that living as long as possible and staying fit are important when thinking about the future (*Quotes 236 and 236*), suggesting that improving life-expectancy is of relevance to patients.

In addition to the previously discussed “extension of a dignified life”, inferred as quality of life in Naumann et al. (2011; *Finding 234*), concepts of longevity and quality of life may merge to form the concept of QALY, which might also be an important concept to consider for the involved stakeholder groups.

3.2.5. *Caregiver-oriented outcomes*

A further recurring theme from the evidence related to outcomes which were caregiver-oriented. They encompass those which pertain specifically to the caregiver, such as burden, caregiver quality of life, the relationship between the caregiver and care recipient, the level of involvement of patients' or caregivers' family in care provision and social support. These outcomes were raised predominantly by the caregivers in the reviewed studies, as may be expected, however patients and healthcare professionals also acknowledged several issues.

3.2.5.1. Caregiver burden

The most recurring caregiver-oriented outcome reported was caregiver burden (also sometimes referred to as caregiver impact), outlined by all three stakeholder groups in a diverse array of methodological approaches, namely semi-structured interviews, focus groups, counselling sessions, tape-recorded diaries and surveys. The outcome was reported in the USA, Brazil, China, Germany, France, Italy, Spain and the UK, indicating some generalisability across these countries. Both AD and MCI participants discussed the outcome, but it was reported predominantly by caregivers, likely because it relates to the caregivers' experiences directly. Of six relevant articles, only one explicitly ranked outcomes for priority (Barrios et al., 2016), while in the remaining 7 studies, the outcome was either assessed for importance using surveys or was raised during qualitative interviews.

Using data quantified from focus groups, Ropacki et al. (2017; *Finding 136*) reported that from their sample of 25 MCI patients, 72% were concerned by the impact their MCI had on the caregiver.

Further, Ropacki et al. (2017; *Finding 142*) reported that 68% of 25 MCI caregivers were concerned by the impact, on themselves, of caregiving for MCI patients. Data from Blieszner and Roberto's (2010) individual interviews with 86 MCI caregivers also raised the issue of caregiver burden (*Quote 137*), relating to a loss of social life as a result of the continued need to provide care, signifying difficulty. Additionally, Gelman's (2010; *Quote 139*) data from counselling sessions conducted with 10 AD caregivers uncovered the overwhelming burden of care for some individuals, with data outlining an accumulation of burdening factors, including caregiving when ill, caring for children in addition to the AD patient, and exhaustion, which led to the participant asking if they were “beyond help”. The 14

AD caregivers in Pavarini et al. (2008) also discussed the difficulty of caregiving (*Quote 150*), stating it is tiring, both physically and mentally (*Quote 151 and 152*), stressful (*Quote 154*), and outlined the difficulties of caregiving when ill or looking after children (*Quote 153*). Subsequently, survey data from 250 AD caregivers (Jones et al., 2010; *Finding 140*) outlined that 34% had to reduce their working hours, with a reported 35-51% loss of free time as a result of caregiving, and participants describing their role as difficult, exhausting, demanding, stressful, frustrating and depressing. Caregivers spent on average seven hours per-day, six days per-week providing care, emphasising burden via the pressing time-commitments of caregiving (*Finding 141*). The ten MCI caregivers involved in interviews in Lu and Haase (2009) outlined feelings of shock, anger, guilt, anxiety, frustration, sadness, loneliness, helplessness, worry and uncertainty, all pertaining to burden (*Finding 143*). In 57 tape-recorded diaries collected in Cheng et al. (2016), an AD caregiver discussed burden increasing in relation to the caregiver's age, as strenuous tasks became harder (*Quote 138*). Further, the 14 caregivers in Lenardt et al. (2010) discussed having to stop working and studying in order to provide care, giving up hobbies like going to the cinema or shopping mall, devoting most of their attention to care, and stating they have lost their freedom (*Quotes 144, 145, 146 and 147*).

Contrastingly, 33 MCI caregivers (Barrios et al., 2016; *Finding 148*) rated caregiver burden and caregiver depression as the outcomes with least priority overall from a predefined list of 12, signifying differences based on different samples, disease stage, or when compared to other patient-related outcomes (such as patient quality of life or patient mental health). In Barrios et al. (2016), MCI patients ranked patient depression as of significantly lower importance than did the caregivers, with the authors suggesting a “Gift of the Magi” effect, whereby caregivers ranked patient-related outcomes as more important, and patients ranked caregiver-related outcomes as more important, which is significant given the impact this could have on the patient-caregiver dyad. This may also explain why fewer MCI caregivers (68%) were concerned by caregiver burden in the Ropacki et al. (2017) sample than were MCI patients (72%), but this difference is minimal.

In addition, semi-structured interview data from 13 healthcare professionals in Bronner et al. (2016; *Quote 155*) indicated that “almost all” of the involved professionals saw caregiver burden as an outcome of importance, as many caregivers make the promise in milder stages of AD of continued care, without acknowledging the increased difficulty accompanying disease progression.

3.2.5.2. Family participation in care

A further outcome related to issues surrounding family and their involvement in the care process. This related to family members drifting apart since diagnosis of the illness, an unequal share of caregiving duties and the importance/positives of involving family in the caregiving process. This outcome was discussed by caregivers and healthcare professionals, relating to AD and MCI participants, signifying relevance across the disease spectrum. Importance was evidenced from recurring discussion in counselling sessions, individual interviews from survey data with samples from the USA, Brazil, Iran, France, Germany, Italy, Spain and the UK.

Data from Gelman's (2010) counselling sessions with 10 AD caregivers outlined a scenario where an AD patient's sister no longer kept in contact with the patient and that it was “tearing the family apart” (*Quote 165*). Further negatives were reported by a participant from Blieszner and Roberto's (2010) 86 individual interviews with MCI caregivers, stating that extended family were involved with the financial aspects of care, but did not help with the “dirty work”, and that the family dictated what they wanted without physically being there to help (*Quote 166*). AD caregivers in Pavarini et al. (2008)

stated that they received a lack of “moral support” from extended family members (*Quote 170*), and a caregiver outlined that they no longer received help from their sibling as a result of his mental illness and ability to cope with his mother’s AD (*Quote 171*). Evidently, not every caregiver experienced negativities, as another participant from the same study outlined that they received help from the patient’s son as well as from church goers and neighbours, and an AD caregiver noted that the patient’s sons were there “anytime if needed” in the semi-structured interviews of Bronner et al. (2016; *Quotes 167 and 168*). However, 75% of 250 AD caregivers surveyed in Jones et al. (2010) reported that AD was devastating to caregivers and their families, suggesting the importance of these familial relationships (*Finding 169*).

Interviews with 14 paid, professional caregivers from AD nursing homes in Iran (Yektatalab et al., 2013) outlined the importance of involving family members in the caregiving process, stating that it keeps patients calm and enables their involvement in important care-related decisions (*Quote 172*). Furthermore, 94% of 500 health professionals surveyed in Jones et al. (2010) recognised that AD was devastating to caregivers and their families (*Finding 173*). This data outlines the importance of a strong family network, the related complexities, and the difficulties faced when these relationships break down.

3.2.5.3. Caregiver social support

Caregiver social support was reported by caregivers and healthcare professionals. This outcome pertains to acknowledging the need for social support as a caregiver, the reported benefits of providing support to fellow caregivers via shared understanding, barriers to seeking social support, the importance of seeking social support from family members, and information regarding the support services that caregivers use. MCI and AD participants outlined this issue, pointing to relevance across various stages of the disease. This outcome was reported in China, the UK, Spain, Germany, France, Canada, the USA and Brazil. Data was collected from semi-structured interviews, focus groups, tape-recorded diaries and surveys.

A participant from the tape-recorded diaries of 57 AD caregivers in Cheng et al. (2016) acknowledged the necessity of seeking social support in the event that they were feeling helpless (*Quote 174*) and another discussed the satisfaction and importance of providing comfort to other caregivers, reporting the benefits of sharing mutual understanding of difficulties (*Quote 175*). Further, Dean et al. (2014b) conducted semi-structured interviews with 20 MCI caregivers, with one participant seconding that having a “good rant” with friends is important to maintaining calmness (*Quote 176*). However, one participant outlined stigma as a barrier to receiving social support, stating that her husband “wouldn’t like” to receive support, given the stigma attached to the illness, indicating barriers to social support should be addressed, and that these barriers extend beyond access to services, towards more socially driven concepts like stigma (*Quote 177*). Relatedly, data from 46 AD caregivers using focus groups in Frank et al. (2010) signified the importance of support between spouses when one has AD, with a caregiver stating that support is “the most important thing” (*Quote 178*). Survey data from 614 AD caregivers in Kurz et al. (2008) found that 70% of German and Spanish, and 31-53% of US, French and Canadian caregivers accessed information regarding peer support groups, with 14-61% (dependent on country) of caregivers accessing information about social events for AD patients (*Finding 179*).

Healthcare professionals from the 13 semi-structured interviews in Bronner et al. (2016) outlined building a social network as important, particularly at the onset of AD, given the novel changes that

occur (*Quote 180*). The importance of social support for caregivers was outlined, and the potential barriers to seeking help such as stigma raised an important issue.

3.2.5.4. Spouses' "duty" to care

A further outcome reported by all three stakeholder groups was the belief that it is the "duty" of the spousal caregiver to provide care to their ill partner, as a result of the marital bond. This relates to data where one partner directly states that a spouse should care for their ill partner, or when a healthcare professional acknowledges this dynamic. This outcome was uncovered from qualitative research, including semi-structured interviews and tape-recorded diaries, and was outlined by AD participants only. It was reported in China, the USA and Germany, indicating relevance in the included countries.

Using semi-structured interviews with a sample of 5 AD patients, an AD suffering wife in Bronner et al. (2016; *Quote 132*) stated that a husband and wife should care for one another; and in this case, the husband was happy to.

Cheng et al. (2016) collected data from 57 AD caregivers using tape-recorded diaries and noted that although one caregiver's husband needed constant care, would visit the toilet throughout the night and would ask questions repeatedly, she would remember that she loved him and "in sickness and health" would provide care (*Quote 134*). Importantly, data from Gelman's (2010) counselling sessions with AD caregivers (*Quote 133*) uncovered a profoundly negative experience, where one husband stole from, "cheated on" and did not care for his wife when she had cancer, however, the wife assumed the responsibility of caring for her AD diagnosed husband, stating "...what would people say?". This indicates that spousal caregiving is not always positive and that some partners may assume caregiving responsibility despite the burden this can cause as a result of the complex marital bond.

Additionally, data from semi-structured interviews with 13 healthcare professionals in Bronner et al. (2016; *Quote 135*) outlined that duties change completely when a spouse is diagnosed with AD, with healthcare professionals acknowledging that the learning process from being a spouse to a caregiver can be "very difficult" in some cases. Although this is not an outcome in the medical or biological sense, it is a profoundly complex issue that should be addressed.

3.2.5.5. Quality of the patient / caregiver relationship

Related to social support, a further recurring outcome, outlined by MCI and AD participants, was the quality of the relationship between the patient and the caregiver. This related predominantly to the strain AD and MCI places on marital and parental relationships and was outlined by both patients and caregivers. This outcome was raised in qualitative research, involving individual interviews, focus groups and observation and was reported in samples from the USA, Canada, China and Denmark.

Interview, focus group and observational data in Hulko (2009) emphasised this strain, as an AD patient discussed feelings of abandonment by their spouse, together with feelings that their spouse and daughters did not understand their condition (*Quote 158*). In accordance, during individual interviews with 11 AD patients in Sorensen et al. (2008), a patient described resentment at being corrected by their spouse, feelings of not being appreciated, and the idea that he was "no longer the man she married" (*Quote 159*). From the same article, however, other patients described their continued happy marriage, and the fear of relationships deteriorating between spouses/children, with another patient acknowledging that they "think it is worse for" their caregiving husband (*Quote 161*).

Further, an MCI caregiver from Blieszner and Roberto's (2010) 86 interviews described the impact of having a marital relationship for 20 years, which is suddenly taken by an illness, stating "I don't know what to do with him" (*Quote 162*). Additionally, during open-ended interviews with 10 MCI caregivers in Lu and Haase (2009), a caregiver reported that their spouse's MCI was costly to their marriage, with a second participant stating they had lost their best friend, in this case her husband (*Quote 163*). This data emphasises the complexities of familial relationships and the different dynamics that influence their quality, with reference to the potential destruction of relationship dyads, or the fear that this may occur.

3.2.5.6. Caregiver quality of life

A final caregiver oriented outcome was caregiver quality of life. This outcome was reported by MCI and AD caregivers and was ranked for importance from a predetermined list, or was assessed in surveys regarding caregiver quality of life. Participants were from the USA, France, Germany, Italy, Spain and the UK.

In Barrios et al. (2016), of the 33 assessed MCI caregivers, caregiver quality of life was ranked as the third most important outcome, ranked after patient quality of life and patient self-efficacy (*Finding 156*). Further, the 250 surveyed AD caregivers in Jones et al. (2010) frequently reported significant changes to their lifestyles, the emotional impact of caring, diminished freedom and physical burden (*Finding 157*). Although this outcome was not discussed in major depth in comparison to others, one can assume that the previously discussed outcomes would have a profound impact on the quality of life of the caregiver.

3.2.6. Health / social care and treatment-related outcomes

The related outcomes refer specifically to healthcare, social care services or to treatment, covering a broad range of topics including stability or control of associated symptoms of AD across the spectrum, limiting medication side-effects, certainty of diagnosis and delaying entry into care homes, in addition to access to health services and information provision. These outcomes were raised mainly by patients and carers.

3.2.6.1. Health services and disease information

The most frequent healthcare and treatment-related outcome related to accessing health services and disease information. This was discussed by the three stakeholder groups extensively, by both AD and MCI participants, and was addressed in samples from the UK, the Netherlands, Canada, Brazil, France, Germany, Spain, Italy, the USA and China, indicating a broad cross-country representation. Caregivers discussed this topic in most depth. The relevant data was collected using a diverse array of qualitative and quantitative methods including focus groups, semi-structured interviews, and surveys, counselling sessions, individual interviews and tape-recorded diaries.

A patient with MCI from the 23 semi-structured interviews of Dean et al. (2014b) stated dissatisfaction at receiving multiple medical tests without receiving information as to why, describing the process as "ping-pong" with no real idea where the "results are going to" (*Quote 202*). This idea of poor information provision was discussed by an AD patient in the focus groups of Kunneman et al. (2017), stating that they arrived home after a short appointment following diagnosis feeling that they had missed a lot of information (*Quote 203*). Further, an AD patient in the 13 semi-structured interviews

of Bronner et al. (2016) stated that the disease was a “mystery” to them, with no idea of the impact of the disease. This uncertainty was seconded by an AD patient in Hulko (2009) following observational sessions, focus groups and individual interviews. Both stated that their limited experience with the disease led them to have a poor idea of the prognosis (*Quote 206 and 207*). Quantitative survey data from 502 AD patients in Kurz et al. (2008) showed that the services used most by patients in the USA and Europe were local peer-support groups and those providing information about treatments for AD, with the most common reasons for not using these services being lack of time, distance/convenience of attending the service or patients not wanting to talk about their AD (*Findings 204 and 205*).

The profoundly negative list of experiences continued with caregivers. During counselling sessions with 10 AD caregivers (Gelman, 2010), a participant stated that they visited a doctor numerous times, reporting that the patient was deemed to be “normal”, with no advice provided on sources of help (*Quote 208*). Another caregiver stated that their community needed more information about AD to help people understand the condition, reporting that “you wouldn’t believe” the level of understanding among her family members (*Quote 210*). From the 86 semi-structured interviews with MCI caregivers in Blieszner and Roberto (2010), a caregiver stated that they used the internet to access information about the disease and now believed they knew more about the condition than the healthcare professionals they had visited (*Quote 211*). Dean et al. (2014b) conducted semi-structured interviews with 20 MCI caregivers, with a participant noting they were “blanked” in a medical appointment, stating that they had to interject to provide information about the medical history of the patient, while other caregivers stated that the information they received was not relevant or applicable, and another that communication was “really poor” (*Quotes 212, 213, 214 and 215*). Dai et al. (2013) reported from their semi-structured interviews with 13 MCI caregivers that a “trigger” was often required, such as a newspaper advert, to prompt seeking medical attention for patient symptoms, indicating poor prior knowledge of the disease, with another participant stating that AD symptoms are a normal part of ageing (*Quotes 217 and 218*). In the 14 AD caregiver interviews in Pavarini et al. (2008), a participant also stated that they attributed deficits to memory and functioning as a product of normal ageing (*Quote 223*). Further, survey data from 250 AD caregivers (Jones et al. 2010) reported that 66% believed the government does not invest enough money into creating new treatments and is a barrier to the development of treatments, 57% agreed that healthcare policy makers are not interested in AD, 64% believed that most people would not know the difference between early AD symptoms and normal ageing, and 66% believed that most people would not recognise the early signs of AD (*Findings 220 and 221*). Of the 614 AD caregivers surveyed in Kurz et al. (2008), the services used most in their samples from the USA and Europe were accessing information about AD and about research and treatments, emphasising the importance of information provision (*Finding 222*). Although this negative data is reported throughout the text, Cheng et al. (2016) reported from 57 tape-recorded diaries with AD caregivers that a patient was extremely happy with the care provided, stating that everywhere they attended, the staff were always “very nice”. In the semi-structured interviews of Dean et al. (2014b), an MCI caregiver acknowledged that doctors are not “superhuman” and cannot provide all the answers (*Quotes 213 and 219*).

Healthcare professionals also outlined a lack of patient and caregiver understanding of AD, as participants in Bronner et al. (2016) stated that people “struggle... to have a basic understanding” of the disease (*Quote 224*), and that caregivers do not understand how serious the disease becomes in the later stages (*Quote 225*). Further, survey data from 500 healthcare professionals in Jones et al. (2010) showed 77% believed that most people would not know the difference between the early

stages of AD and normal ageing and 70% believed that most people would not recognise the early signs of AD (*Finding 227*). Further, 50% believed the government does not invest enough in treating AD, 29% that the government was a barrier to finding new AD medications and 36% that healthcare policy makers are not concerned about AD (*Finding 226*). This data evidences the importance of information provision regarding AD across the spectrum and the need for improved patient/caregiver-healthcare professional interactions with respect to information provision.

3.2.6.2. Stability of symptoms and general symptom control

A further outcome pertained to stability / control of symptoms associated with AD across the spectrum. This was outlined by the three stakeholder groups, by AD participants only. It was addressed in samples from the USA, Canada, Brazil, France, Germany, Spain and Australia, and was discussed primarily by caregivers. Evidence supporting this outcome was based on discussions surrounding symptom stability/control, relating specifically to treatment expectations, or controlling symptoms at a level that enables functionality (hence related to treatment). It was derived from surveys, ranking of outcomes and semi-structured interviews.

Of the 502 AD patients surveyed in Kurz et al. (2008), 72-98% outlined better control of AD symptoms as an important treatment outcome (*Finding 181*).

In accordance with this, the four AD caregivers involved in the semi-structured interviews of Andersen et al. (2008) stated that they expected treatment to “hold” the AD patient in their current state and to prevent the patient from deteriorating further, signifying stability of symptoms (*Quotes 182 and 183*). Relatedly, the six AD caregivers involved in the semi-structured interviews of Smith et al. (2008) stated that they wanted to keep AD progression “steady” to stabilise the patient and acknowledged that the patient would never be healed or regain the functioning they had lost, but could be stabilised (*Quotes 184 and 185*). Further, narrative interviews with 17 AD caregivers in Smith et al. (2011) noted that a caregiver expected a vast improvement in AD symptoms from treatment (*Quote 186*), but acknowledged that this was naïve and was impressed by the stability the drugs provided. Additionally, the 35 AD caregivers in Naumann et al. (2011) ranked “slowing down the progression of AD” as the fifth most important outcome of 25, ahead of outcomes such as keeping the patient out of care and improving behavioural symptoms (*Quote 187*).

Of the 11 healthcare professionals in Andersen et al. (2008), a nurse stated that an “expectation” of treatment would be to stabilise the patient, allowing them to stay at home for longer, and a physician stated they would expect stability, allowing for “some months” at a level of functioning unachievable without medication (*Quotes 188 and 189*). The evidence surrounding this outcome suggests importance, with no conflicting viewpoints between stakeholder groups.

3.2.6.3. Delaying entry into institutional care

AD patients, caregivers and healthcare professionals also discussed delaying entry into institutional care in samples from Canada and Germany, incorporating semi-structured interviews and surveys. This outcome related to statements where a participant explicitly stated that they want to delay entering a nursing home, or to stay in their own home for as long as possible. This outcome overlaps closely with patient independence, however, given the discussion surrounding treatment, health and social care in the reviewed literature, this outcome was deemed to fit closer to the present theme.

An AD patient in MacRae (2008; 2010) stated that they wanted to “stave...off” entry into a nursing home for as long as possible (*Quote 198*).

The 35 AD caregivers in Naumann et al. (2011) ranked “delaying entry into care”, “preventing the patient going into care”, and “keeping the patient at home for longer” as the 6th, 7th and 8th most important outcomes out of 25 (*Finding 199*).

A nurse in Andersen et al. (2008) stated that treatment should stabilise the symptoms of AD, allowing the patient to stay at home for longer (hence delaying entry into care; *Quote 200*) and a healthcare professional in Bronner et al. (2010) stated that relatives of AD patients would like to keep them in their own home for as long as possible (*Quote 201*). This outcome was outlined by the three stakeholder groups, however, it is vitally important to consider the implications this has on the caregiver. With reference to the “spouses’ “duty” to care” outcome, particularly the work by Gelman (2010), a caregiver may take-on an unhealthy level of burden to keep a patient in their own home with detriment to themselves. This highlights the need to consider the complexities of patient-caregiver relationships when determining outcome priorities.

3.2.6.4. Medication side-effects

Limiting the side-effects of medication was discussed by AD patients and caregivers and was measured in samples from the USA, Canada, Brazil, France, Germany and Spain. This outcome related specifically to surveys assessing the importance of limiting medication side-effects, without specifically defining what these side-effects are.

Of the 502 AD patients surveyed in Kurz et al. (2008), 63-96% (dependent on location) outlined “fewer bothersome side-effects” of medication as an outcome of high priority (*Finding 190*).

Furthermore, 84-100% of 614 AD caregivers in Kurz et al. (2008) rated “fewer bothersome side-effects” of medication as an outcome of high priority (*Finding 191*). Oremus et al. (2015) assessed willingness-to-pay with 216 AD caregivers using a number of hypothetical treatment scenarios, noting that treatments with no adverse side-effects were 3.4 times more likely to be supported than those with a 30% chance of side-effects (*Finding 192*).

3.2.6.5. Certainty of diagnosis

AD and MCI patients and caregivers from the Netherlands and UK discussed the accuracy and certainty of diagnosis of the disease during semi-structured interviews and focus groups. This outcome was apparent in participant quotes and related to diagnostic testing and discussion of diagnosis with healthcare professionals.

In Dean et al. (2014b), the 23 MCI patients involved in semi-structured interviews discussed the relief of having a firm diagnosis, also stating that they prefer to “know” rather than “think” of the cause of their symptoms (*Quotes 193 and 194*). Further, in the focus groups with MCI and AD patients in Kunneman et al. (2017), participants stated they are pleased to have a clear diagnosis as it allowed them to try and do something about their illness, however, one patient expressed dissatisfaction at their diagnosis, stating they were missing information following a “short conversation”, signifying the importance of addressing diagnosis sufficiently (*Quotes 195 and 196*).

Further, one of the six AD caregivers in Kunneman et al. (2017) expressed satisfaction with lumbar puncture diagnostic testing as it was felt to give a certain diagnosis of AD (*Quote 197*), suggesting there may be a preference for diagnostic methods which provide a definitive answer.

3.2.7. Social Issues

“Social issues” encompass outcomes relating to the public perception of AD across the spectrum, and the ways in which public opinion may implicate key stakeholders, for example, the anticipated and perceived stigmatisation associated with receiving a diagnosis of MCI or AD.

3.2.7.1. Stigma

This refers to stakeholders’ experiences of anticipated, perceived or actual labelling or stereotyping as a result of the AD disease process, alongside the emotional, psychological and societal effects of experiencing such stigmatisation. This outcome is informed by qualitative data, deriving from patients and caregivers in Canada, China and the UK, though limited patient data from Canada also reported this outcome.

During an in-depth interview in Canada, a patient with early-AD discussed the necessity of “properly informing” the public about dementia in general, so it can stop being perceived as a ‘shameful’ disease and instead can be considered as equivalent to ‘a broken arm or leg’ (MacRae, 2008; 2010; *Quote 127*). Similarly, caregivers acknowledged the stigma surrounding dementia, and admitted that it had acted as a barrier to seeking social support (Dean et al., 2014b; *Quote 131*). Although, these quotes demonstrate the stigmatised nature of AD across Western communities, the majority of evidential support for this outcome was derived from research conducted in China.

Caregivers in China describe various unpleasant aspects of experiencing stigmatisation including the uncomfortable looks from the public, the embarrassment of caring for a family member with AD, the inability to accept the diagnosis and the unhappiness surrounding the naming of an AD diagnosis in China – “laonian chidai”, literally meaning “stupid, demented elderly” (Cheng et al., 2016; Dai et al., 2013; *Quotes 128, 129 and 130*). The greater discussion surrounding stigma by Chinese caregivers could be underpinned by this degrading naming, but it is equally important to note that the Latin etymology for dementia is similarly demeaning (“being out of one’s mind”). Nevertheless, this clearly highlights the importance of encouraging the discussion of psychiatric health in a considered and sensitive manner.

3.3. Secondary analysis: which outcomes of AD across the spectrum are prioritised by stakeholder subgroups?

In addition to the primary analysis aimed at uncovering priority outcomes from patients, caregivers and healthcare professionals, two secondary considerations are outlined, namely:

- 1) Comparing patient, caregiver and healthcare professional outcomes based on AD stage;
- 2) Comparing outcomes based on caregiver demographics, e.g. spousal, adult children, or older and younger adults based on the different dynamics this may create, like caregiving when in employment or when the caregiver themselves has an illness.

It is important to note that any interpretations are limited by the body of research uncovered by the present review.

3.3.1. Alzheimer's Disease stage

Initial investigations aimed to compare outcomes based on the various stages of AD, such as mild-moderate-severe, however, no late-stage AD patient samples were identified among the studies included in our SLR. Of the included articles, six specified that the involved AD patients had mild AD (Andersen et al., 2008; Beard et al., 2009; Kunnehan et al., 2017; MacRae, 2008; 2010; Sorensen et al., 2008), while six specified mild-moderate AD (Cheng et al., 2016; Frank et al., 2010; Kurz et al., 2008; Lenardt et al., 2010; Malthouse and Fox, 2014; Oremus et al., 2015). All other studies specified AD or MCI only. For this reason, comparisons for the varying stages of dementia caused by AD (mild-moderate-severe) were not appropriate given the unreliability that an outcome corresponds to one specific AD stage due to overlapping participants: Therefore, it was more appropriate to compare AD and MCI participants only. It is important to note that AD stage was not always defined in the reviewed articles, and in many cases participants were referred to as AD or MCI patients. As MCI can be caused by AD, and AD samples may include both MCI and dementia patients, interpretations here are limited. This section of the analysis aimed to provide a general look at the outcomes which were discussed by earlier stage MCI patients and more advanced stage AD patients. It is necessary to acknowledge the limitations of doing this with the presently reviewed literature to avoid misleading reporting.

3.3.1.1. Patients

Ten of the included studies involved participants diagnosed with or referred to as “AD patients” and eight involved participants diagnosed with or referred to as “MCI patients”. From these samples, a total of 19 AD and 17 MCI patient outcomes were uncovered.

Twelve outcomes were outlined by AD patients across the spectrum, namely: memory/slowing of forgetfulness, patient mental health, patient independence and autonomy, patient social engagement, physical health, judgement and insight, access to health services and disease information, activities of daily living, certainty of diagnosis, maintaining identity of personality and stigma.

AD diagnosed patients (but not MCI) outlined the following outcomes: delaying entry into care, spouses “duty” to care, quality of patient-caregiver relationship, stability of symptoms and general symptom control, medication side-effects, patient quality of life and length of patient life. MCI diagnosed patients (but not AD) also outlined the following outcomes: driving, language and communication, executive functions, patient sleep patterns and caregiver burden.

One interpretation may be that outcomes such as delaying entry into care, stabilising symptoms and increasing the length of patient life were outlined by AD patients as these factors pertain to the progression of the illness and the likelihood of entering care heightens as the disease progresses. However, outcomes such as caregiver burden would likely increase, too, but this was reported only by MCI patients. An explanation for this may be that earlier stage patients are concerned about their relationship with and the wellbeing of the caregiver early in the disease, whereas when the disease progresses, caregivers will have learnt to cope with this and patients’ focus of their concerns shifts towards their own wellbeing. Relatedly, outcomes such as driving and executive functions could be more important to MCI patients as their impact may be more associated with earlier disease stages,

i.e., it is less likely that a patient with moderate or severe AD would still be driving, or concerned with or aware of, decline in executive function.

3.3.1.2. Caregivers

Of the included studies, 14 involved participants referred to as “AD caregivers” and seven included participants referred to as “MCI caregivers”. A total of 19 outcomes were specified for the AD caregivers and 26 for the MCI caregivers, despite the smaller number of included articles.

Fifteen of the outcomes were outlined by AD caregivers across the spectrum, namely: challenging and distressful behaviours, patient independence and autonomy, memory/slowing of forgetfulness, activities of daily living, stigma, spouses “duty” to care, caregiver social support, health services and disease information, patient quality of life, caregiver quality of life, caregiver burden, patient mental health, language and communication, medication side-effects and maintaining identity or personality.

The “AD caregiver” samples (but not MCI) discussed the following: delaying entry into care, stability of symptoms and general symptom control, eating behaviours and certainty of diagnosis, whereas the “MCI caregiver” samples (but not AD) outlined the following outcomes: driving, judgement and insight, patient self-efficacy, maintaining patients’ hobbies, patient apathy, patient sleep patterns, quality of the patient-caregiver relationship, family participation in care and general cognitive health.

Akin to the patient outcomes, interpretation may be that delaying entry into care, stabilising symptoms and eating behaviours were outlined by AD caregivers as these factors pertain to the progression of the illness, i.e., symptoms and lack of functioning increases and the likelihood of entering care heightens as the disease progresses. Certainty of diagnosis may have been outlined by AD caregivers, given the severity and irreversibility of the condition (while MCI may not progress to AD or dementia), so a definitive diagnosis is arguably more crucial here: however, the issue of diagnostic certainty was discussed by both AD and MCI caregivers. Relatedly, outcomes like driving, self-efficacy and maintaining hobbies may be more important to MCI caregivers, as they are associated with earlier disease stages, i.e. it may be unlikely that a patient with more severe AD would be driving anymore or partaking in complex hobbies.

3.3.1.3. Healthcare professionals

No studies assessed the opinions of healthcare professionals regarding MCI, hence, a comparison could not be conducted for this stakeholder group.

3.3.2. Caregiver comparisons

Initial considerations aimed to compare spouses to adult child caregivers, with the belief that spouses would likely be older, facing their own illnesses and adult child caregivers would be working or have younger children in addition to caregiving, i.e., “sandwich generations”. The nature of the reporting in the included studies did not allow for detailed differentiation between these groups. Most analyses were conducted including all caregiver types collectively, with the construction of salient themes derived from a combination of all participants not accounting for subgroups, or, all caregivers were referred to collectively with terms like “family support persons” (Beard et al., 2009). Articles by Lu and Haase (2009; 2011), Malthouse and Fox (2014) and Smith et al. (2008) included spousal caregivers only, however, there were no comparison groups such as adult children, therefore, one could not say conclusively that an outcome was related to spouses only. Further, older caregivers, e.g. in Gelman

(2010), discussed having to work and care for grandchildren, so there was crossover between the roles in caregiver groups (i.e., not only middle-aged adult children had to work or look after dependents). Caregivers varied in age, ranging from 25-92 years (Blieszner and Roberto, 2010; Smith et al., 2008); however, there was no reliable or valuable way to compare outcomes for younger and older caregivers. Given the context of participant quotations in some articles, however, some interesting distinctions could be made.

Importantly, some data could be extracted to outline the difficulties of;

1. Caregivers who are employed or care for dependent children, and;
2. The difficulties of caregiving as an older person.

3.3.2.1. Caregivers who are employed or care for dependent children

A daughter of an AD patient in Blieszner and Roberto (2010) stated that multiple stressors made her “blow a fuse” as she was caring for her baby, whilst caring for her ill mother, and her husband could not help. This participant also discussed not trusting her mother to look after the baby with fear that something would go wrong (*Quote 238*). Further, an elderly caregiving wife in Gelman (2010) stated that she could no longer work due to her spouse’s AD and his need for care, which was threatening the loss of her husband’s health insurance, reporting \$60,000 of debt (*Quote 239*). Further, a second elderly caregiver in Gelman (2010) discussed the issue of having to care for her daughter’s young children in addition to her ill mother (*Quote 244*), hence, providing evidence for a different dynamic whereby an elderly caregiver cares for her ill mother and her grandchildren because her daughter must work. A caregiver in Lenardt et al. (2010) also stated that they had to stop working and studying so that they could provide care (*Quote 241*), and an AD caregiver in Pavarini et al. (2008) also stated that they gave up work when they found out their mother had AD (*Quote 242*). A second caregiver discussed being extremely distressed with depression, taking medication, and outlined that the stress and burden would be lessened if she did not have to provide for a son, daughter-in-law and grandchild (*Quote 243*). A son of an AD patient in Cheng et al. (2016) discussed having to stay away from home until late so he could help feed his father dinner but expressed that his children showed understanding. This data emphasises the difficulties faced by those who work, study and/or care for children in addition to their ill family member. It also signifies that being an older spousal caregiver and being a worker or carer to dependent children are not mutually exclusive (*Quote 240*).

3.3.2.2. Implications of caregiving as an older person

Despite a subgroup of the previously discussed research relating to elderly patients, issues surrounding caregiving as an older person *specifically* were apparent in the included articles, relating to caring whilst dealing with an illness, having the fear that the caregiver themselves will begin to suffer from AD or a related disorder and worry that the patient could be left on their own should the caregiver die.

An elderly AD caregiver in Gelman (2010) stated that she and her elderly sister both had arthritis and could “barely walk”, signifying the difficulties of caregiving when sick (*Quote 244*). A spousal caregiver in Dai et al. (2013) also discussed having cancer, diabetes and prostatitis, stating concerns about “getting older” and who would care for them both in the future with the hope that they go into care together (*Quote 247*). Further, a caregiver in Blieszner and Roberto et al. (2010) expressed worry at taking care of their partner whilst “having some sort of ailment”, and the issues surrounding “seniors

taking care of seniors” (*Quote 245*). A second caregiver in this study discussed worry at what would happen to the MCI patient if the caregiver was to die, stating that they would be left alone with no one to care for them. This subtheme again raises important issues to consider when addressing the complexities of the patient-caregiver relationship.

Although this may not help determine which outcomes are of priority to the stakeholder groups, it raises the importance of determining the circumstances or demographics of the caregiver before targeting an outcome of priority, for example, an elderly patient may receive limited help from their older family, in addition to having the belief that it is the spouses’ “duty” to care whilst delaying entry into a care home without truly understanding the burdening implications of assuming this responsibility, in line with comments made by healthcare professionals in Bronner et al. (2016) (*Quotes 82 and 135*).

3.4. Primary analysis: what do stakeholders believe constitutes a meaningful delay of AD across the spectrum?

With respect to meaningful delay in disease progression for AD and MCI, the included studies provided information about three categories, namely cognition, health / social care and treatment-related outcomes, and functioning / dependency. These encompassed the four outcomes of memory and slowing of forgetfulness, stability of symptoms and general symptom control, change on the ADAS-Cog and activities of daily living. In comparison with the first question, evidence to address the specific issue of meaningful delay was sparse, with most data deriving from healthcare professionals and limited data from patients or caregivers.

3.4.1. Cognition

As stated previously, the category ‘cognition’ encompasses symptomology relating to cognitive functioning, such as memory, language, communication, executive functions, judgement and insight. Discussion of meaningful delay for the present research question focussed on memory and slowing of forgetfulness and what constitutes a clinically meaningful change on the ADAS-Cog.

3.4.1.1. Memory / “slowing of forgetfulness”

Patients and healthcare professionals from Canada in Andersen et al. (2008) discussed delay of memory deterioration in relatively vague terms, however, the data provided enough evidence to suggest the importance of delay in this area.

One of the four included patients stated during a semi-structured interview that they wanted to slow down the rate of memory decline by “quite a bit” (*Quote 248*), which, despite being vague, suggests that significantly slowing the rate of memory decline would constitute a meaningful delay.

Further, healthcare professionals in Andersen et al. (2008) noted that they would expect treatment to slow deterioration of memory loss impacting daily functioning, with another stating that delay to general cognition and memory is expected (*Quotes 249 and 250*), suggesting that delay to these areas would be meaningful. Again, while this does not offer much help in determining what would be a meaningful delay, it outlines important areas.

3.4.1.2. Change on the ADAS-Cog

Healthcare professionals were involved in two studies evaluating what would constitute a meaningful change on the ADAS-Cog with AD patients.

In one study (Rockwood et al., 2010), researchers compared ADAS-Cog results to those of patient, caregiver and clinician goal attainment scores (PGAS and CGAS) and a Clinical Global Impression of Change-Plus Caregiver Input (CIBIC+), to determine whether a 4-point change on the ADAS-Cog represents meaningful change in disease progression among AD patients. The ADAS-Cog is often referred to as a pivotal trial endpoint (e.g. Qaseem et al., 2008), so it is important to determine how much of a change would be meaningful, and if this change is consistent across measures.

The researchers found that at the group level, change was consistent across the measures, i.e., a significant change on the ADAS-Cog corresponded to a significant change on the CIBIC+ *overall*.

At the *individual level*, however, there was only about 50% agreement across the involved measures. This means that only 50% of patients showed agreement on all measures (i.e., a significant change on the ADAS-Cog did not always correspond to a clinician's impression of change or measures of goal attainment). This highlights that detecting meaningful change or improvement using measurements like the ADAS-Cog may not be reliable at the individual level (*Finding 251*).

Further, Schrag and Schott (2011) conducted a similar study to determine the minimally clinically relevant change on the ADAS-Cog (it is important to note that the differences between minimal clinically relevant change and meaningful delay in disease progression are understood by the researchers, however the methodology used emphasises the discrepancies and the potentially arbitrary nature of using cut-off points on clinical measures to denote significant change, which may be translated to delay). The study used an anchor based method with clinicians to determine a clinical impression of change, which was compared to ADAS-Cog scores. Minimal clinically relevant change was determined to be 3 points in this instance (*Finding 252*).

3.4.2. *Health / social care and treatment-related outcomes*

The related outcomes refer specifically to health and social care services or to treatment, in this instance, referring only to stability or control of associated AD symptoms.

3.4.2.1. Stability of symptoms and general symptom control

Meaningful delay in this instance was outlined by caregivers and healthcare professionals in Andersen et al. (2008), relating that general control of symptoms would relate to a meaningful delay in disease progression.

Two caregivers stated that they wanted to “hold the patient” where they are, indicating that no-change in symptomology would be a meaningful delay (*Quotes 253 and 254*).

Further, healthcare professionals noted that stability in symptoms would allow the patient to stay at home for longer (*Quotes 255 and 256*), suggesting that symptom control and indeed staying out of care would be a meaningful delay from a healthcare professional's experience. Again, despite the data being minimal here, it may give an indication of the relevant areas where delay may be important.

3.4.3. Functioning and dependency

The category is represented by discussion of maintaining patients' ability to function independently and successfully in day-to-day life.

3.4.3.1. Activities of daily living

Here, meaningful delay was discussed by a healthcare professional in Andersen et al. (2008), where a pharmacist stated that improvement to ADLs living via maintaining the ability to dress themselves (buttoning a shirt or fastening the zip on a jacket) would be meaningful (*Quote 257*).

4. Discussion

4.1. Summary of findings

This systematic review aimed to ascertain which “real world” outcomes of AD across the spectrum are considered most important to patients, caregivers and healthcare professionals. Secondly, we aimed to identify, from the perspective of the key stakeholders, what constitutes a meaningful delay in disease progression of AD across the spectrum. A robust and systematic review process was undertaken to address these research questions.

4.1.1. Details of priority outcomes for Alzheimer’s disease across the spectrum

A list of outcomes of AD across the spectrum was produced, which aligned closely with previous WP2 activities (Deliverable 2.1). In light of the largely inferential synthesis process and overlap in outcomes between categories, it is not possible to ascertain an explicit hierarchical structure of these outcomes in order of importance. Nevertheless, the consistent appearance of a sub-set of outcomes appeared in studies of all three stakeholder groups was taken to infer their relative importance. Eight outcomes emerged as the most consistent: memory/ slowing of forgetfulness, activities of daily living, independence and patient autonomy, mental health, maintaining identity or personality, caregiver burden, health services and disease information, and patient quality of life.

“Memory” emerged as a key outcome, alongside “slowing of forgetfulness” as a prioritised treatment outcome. Outcome measures of memory, and general cognition, are typically gathered during clinical trials using the ADAS-Cog or MMSE. Although the sensitivity of these instruments for assessing particular disease stages have been questioned, they are generally regarded as important outcome measures in clinical trials for AD (Posner et al, 2017). Our findings reinforce the notion that cognition – particularly memory – should continue to be considered a priority outcome of AD across the spectrum in future research.

In addition, activities of daily living – typically implicated by deficits in memory – was a consistently endorsed outcome. In particular, caregivers stressed the importance of such functional outcomes, presumably as patient deficits in daily functioning can result in substantial burden for the caregiver. Currently, there are multiple measures of functional capacity which may be utilised in clinical trials (such as the Activities of Daily Living Questionnaire; Johnson et al, 2004 or the Alzheimer’s Disease Cooperative Study – Activities of Daily Living [ADCS-ADL]; Galasko et al., 2006). Our findings reinforce the importance of including such measures to evaluate treatment efficacy. This review also identified a specific subset of daily activities which were considered most important to stakeholders, including independent use of the toilet, eating meals, maintaining hobbies, driving and practising self-hygiene. This suggests that it may be important to apply additional weight to these items during functional evaluations.

Furthermore, “independence and patient autonomy” was one of the most consistent outcomes to derive from this review. As a construct within AD across the spectrum, dependence is multi-faceted and typically interrelated with physical functioning, thus, the validity of dependence as a health outcome measure has been questioned (Spackman et al, 2013). Nonetheless, this review identified

independence and autonomy among patients, caregivers and professionals alike, suggesting that such an outcome should be at the forefront when developing treatment trials.

“Mental health” similarly emerged as a key outcome reported by all stakeholder groups, particularly in relation to depressive and anxious symptoms. Moreover, the subjective importance of mental health as an outcome derived from participants who were diagnosed with, caring for or treating the earlier stages of the disease process. Whilst this highlights the importance of measuring mental health outcomes in future research trials, it also infers that this should be of greatest importance when recruiting samples with MCI or early-AD. This observation may be underpinned by the negative emotional effects of receiving a diagnosis, adjusting to new limitations, and dealing with an uncertain fate. Whilst uniformity of outcome measures across research is crucial for successful treatment development, this finding equally suggests that subtle discrepancies in outcome priorities between those in or caring for patients in different stages of disease progression should be taken into account. Although, in this instance, it is also important to consider the complex relationship between depressive symptoms and cognitive impairment. Depression is often considered as a key feature of prodromal AD (e.g. Sun et al, 2008) and as a general risk factor for cognitive impairment (Green et al, 2003; Herbert & Lucassen, 2016). Thus, the utilisation of depression as a key outcome may artificially inflate error rates. Therefore, albeit highly important in disease progression, depression may not offer enough specificity to be considered as a primary outcome measure.

“Patient quality of life” emerged as a recurring outcome and was mentioned by patients, carers and healthcare professionals. This outcome is documented extensively with regards to AD research, through measurement, interventions and discussion of its implications as an outcome (e.g., Dooley and Hinojosa, 2004; Riepe et al., 2009), hence, it was likely this would emerge as an outcome of importance. In the reported data, patients expressed wanting to live a fulfilling life; with quality of life emerging as an outcome of greatest importance in the survey work of Kurz et al., 2008. Caregivers also expressed the wish to improve patients’ quality of life, and in two studies where priority was explicitly ranked (Barrios et al., 2016; Naumann et al., 2011), caregivers voted quality of life and living a dignified life as the main priority. Healthcare professionals also discussed quality of life with regards to treatment and stated improvement to quality of life is a major expectation. Hence, our findings endorse quality of life as an outcome of importance, and continued efforts in this area are warranted.

A further recurring outcome related to the preservation of patients’ “identity or personality”, particularly deriving from patients, friends and relatives. The unanticipated volume of evidence for this outcome in the reviewed papers highlights the importance of retaining patients’ sense of self. The measurement of this outcome certainly poses practical issues due to inherently subjective interpretations of identity and the fluidity of particular personality traits or characteristics. Nevertheless, the findings from this review suggest that steps should be taken to incorporate this outcome into future research.

The most recurring caregiver-oriented outcome was “caregiver burden”. This was discussed by all three stakeholder groups, but was – unsurprisingly - raised most frequently by the caregivers. Generally, patients expressed concern that their illness was impacting their caregiver(s) negatively, caregivers discussed their burdening experiences and the associated negative emotions, and healthcare professionals discussed the importance of this burden given their experience and knowledge of the impact of disease progression. Caregiver burden, its causes, measurement scales and interventions targeting the issue are well documented in AD research (e.g., Mohamed et al., 2010; Beinart et al., 2012). The question raised is whether caregiver burden is an outcome of priority for AD,

given it is not an outcome experienced by the person with AD directly. The present review would argue that it is, given that caregivers spend most of their days caring, experiencing exhaustion, stress and depression, and are at the forefront of the illness (Jones et al., 2010).

“Health services and disease information” was another recurring theme among patients, caregivers and healthcare professionals. Although not a conventional outcome in the medical sense, its presence in numerous articles and supporting data signified importance. Patients discussed receiving no information regarding medical tests or why they were conducted, and were unclear about their diagnosis and illness pathway. Caregivers expressed a lack of information provided at various health services, that the information provided was not relevant to them and that the communication between healthcare professionals and caregivers / patients was poor. Caregivers also believed the government does not invest enough into treating AD and act as a barrier to new treatments. There was also a lack of knowledge about the disease reported by caregivers, stating the diseases are a normal part of ageing or that they needed prompts (i.e. letters from memory clinics) to “trigger” attending health services, and the majority also believed that most people would not know the initial signs of AD. Healthcare professionals also agreed that understanding of the disease is poor among caregivers and patients, again noting that most people would not recognise the early symptoms of AD, and again, a large group reported that the government does not invest enough into treating AD and that policy makers are not interested in finding new treatments. This poor recognition of the early signs of AD is hugely important given that early and accurate diagnosis of AD across the spectrum has been outlined as a key recommendation for progressing dementia care, treatment and prevention (Scheltens et al., 2016; Winblad et al., 2016). This raises an important issue relating to prioritising symptomology vs. more societal outcomes. Given that accessing health services and disease information was discussed at a similar level to outcomes like memory, activities of daily living and patient independence in the presently reviewed literature, one may ask how much priority should be given to providing AD patients and their caregivers with more information about the illness, or freeing clinicians to spend more time with them in a consultation to ensure patient satisfaction. This might relieve pressure over other important outcomes which are harder to address, or are at this time optimistic given current treatment options. Despite this negative outlook, it is important to note that some caregivers reported positive experiences with healthcare professionals and understood that clinicians do not hold all the answers, however, the consensus was that patient and caregiver understanding of the illness was poor, that information provision was unsatisfactory, and efforts may be necessary to rectify this issue, particularly given the importance of earlier diagnosis (Scheltens et al., 2016; Winblad et al., 2016).

The remaining outcomes, although important as inferred by the present researchers or ranked in the literature by participants, were not supported by as much evidence as those discussed here, and it was difficult to infer their importance or priority in a scientifically fair and open manner. That is not to say that those outcomes were not important or were not supported, but rather, more work is required to determine a hierarchical structure of importance or priority if appropriate, without misleading the reader.

In sum, several of these key outcomes are typically measured in clinical trials, such as cognition and activities of daily living. Thus, it is reassuring to discover that current research protocols reflect the valuable opinions of patients, caregivers and healthcare professionals. However, this review has also unveiled several additional outcomes – not typically assessed in clinical trials – which appear to be of importance to key stakeholders, such as the preservation of patients’ personality or identity, and accessing health services and disease information. Equally, there are a variety of typically employed

outcome measures which were not acknowledged in this review. Considering the growing emphasis on neuroimaging in clinical trials (e.g. Cash et al, 2014), it is somewhat surprising that no stakeholder group regarded objective imaging outcomes, such as amyloid or tau markers, as important outcomes of AD across the spectrum. It is possible that this, and other, relevant outcomes were missed due to the sparsity of data deriving from healthcare professionals in the retrieved evidence base which excluded opinion pieces and clinical or scientific studies. Alternatively, as the evidence linking biomarkers and clinical symptomatology is currently tentative, stakeholders may be most likely to prioritise the outcomes with directly observable and tangible effects in daily life. Despite these uncertainties, this review hopes to provide a potential framework of outcome measures which represent the voices of those most personally implicated by AD across the spectrum.

4.1.2. Details of what constitutes meaningful delay in disease progression

There was limited data reported in the literature for this research question, relating to cognition, functioning and dependency, health / social care and treatment. More research is required in this area before any conclusions can be made, however, the discussion of what constitutes a minimally clinically relevant or meaningful change on the ADAS-Cog raises the issue of discrepancies between what is measured via assessment tools and what is observed clinically, and indeed, that indices of change vary across populations and with the individual (Rockwood et al., 2010). These findings are in line with critiques in the literature surrounding the use of outcome measures and patient reported outcome measures as pivotal endpoints in clinical trials, their sensitivity, and the level of stakeholder input which influence these (e.g. Cano et al., 2010; Delva et al., 2014; Harrison et al., 2016; Posner et al., 2017). To determine what constitutes a meaningful delay in disease progression from the views of patients, caregivers and healthcare professionals, work uncovering “real world” experiences is necessary, in line with discussion from Alzheimer’s Society and government bodies (Alzheimer’s Society, 2013; Seeher et al., 2010).

4.2. Strengths and limitations

Several key strengths of this research derive from the distributed and multi-disciplinary team of researchers who contributed towards this review throughout all stages of the research. Whilst it is possible that some relevant literature may have been missed from the initial search, the robust search strategy – with continued input from expert researchers and clinicians in the field – instilled confidence that we had achieved a comprehensive and relevant literature base, within the time restrictions set. Furthermore, we did not exclude articles based on language limitations, thus allowing for a literature base spanning a widespread geographical profile. Finally, this review was strengthened by the application of multiple analysts at all stages of the research, alongside consistent checks with experts in the field. This multi-disciplinary approach ultimately aimed to improve the rigour and robustness of the research process.

However, there are a number of caveats to this review which must be addressed. Firstly, although our search strategy was suitably broad, it may not have captured all the relevant material. Throughout the search process, individuals with MCI or AD were referred to using the search term “patients”. Therefore, it is possible that relevant articles were missed which utilised terms such as “people”, “person” or “subject”. A post-hoc literature search was conducted to assess the impact of this decision. From just two literature databases, almost 1,000 additional papers were identified with the introduction

of these search terms. Furthermore, while this review aimed to gather the opinions of individuals affected by AD across the spectrum, it is equally necessary to identify the views of patients with other forms of dementia. It is possible that patients with alternative pathologies, and their respective caregivers and healthcare professionals, assign priority to a different set of outcomes. Over 2,500 papers were excluded on the basis of “condition” in this review; whilst a sub-set of these papers may have been valuable, their inclusion would have been particularly time-consuming. Ultimately, these decisions to narrow the search process may have limited the scope of the review, but were arguably decisions of pragmatism in order to reach an achievable volume of articles to screen with the time and resources available.

Furthermore, it is important to acknowledge the methodological heterogeneity which was present throughout the included studies. Whilst the inclusion of a variety of study types is considered a strength of this review, there were a small number of studies which explicitly asked stakeholders to prioritise a set of outcomes. In this approach, a pre-determined set of outcomes is used, meaning that ‘white spots’ (undiscussed areas which may be a priority to people affected by AD) were not included. In the remaining papers, it was necessary to infer the importance of outcomes from quotations and original textual findings. It is possible that this method of analysis may have introduced potential bias as this is essentially an “interpretation of an interpretation” (however, having multiple contributors and data checks will have guarded against this bias). Nevertheless, reviews of qualitative literature are inherently based upon inferential processes and personal judgement. Thus, the resultant interpretations are up for debate. Additionally, research has outlined the benefits of including a mixed-methods body of research (quantitative and qualitative) in systematic reviews, stating that *“the mixed-methods model enables us to integrate quantitative estimates...with more qualitative understanding from people’s lives”* (Harden, 2010). Although our data sources are heterogeneous, this review combines rankings of outcomes and survey work with quotes relating to stakeholder experiences necessary to gain a fuller understanding of the disease (e.g. Carmody et al., 2015), in line with Harden’s (2010) proposed strengths.

There are also a number of important subgroups whose valuable opinions were missed within the included studies. First, there was little evidence which addressed the opinions of patients’, or corresponding stakeholders, at the most severe end of the AD spectrum, including those in palliative care (however, it is difficult to obtain the views of severely affected patients, but important to seek views of their advocates). However, given the time-intensive nature of qualitative work, the need for reliable and coherent communication between the researchers and the participants, and the requirement of appropriate consent procedures, it would be practically and ethically very difficult to conduct such research, particularly for the patient group. Nevertheless, this is an important gap to address. Similarly, this review did not address the opinions of previous caregivers of deceased patients with AD. These individuals encompass an important subgroup of caregivers who have likely been through the entire disease process with the patient and would therefore offer highly valuable opinions. Inversely, there was little evidence representing those with a subjective cognitive impairment. As it is a highly heterogeneous condition, those with subjective cognitive impairment do not always go on to receive a diagnosis of AD, but it has recently been suggested that it serves as a potential precursor and at least a portion of those with subjective cognitive impairment will eventually develop AD (Garcia-Ptacek et al, 2016). In light of these gaps in the literature, it is important to interpret the findings of this SLR with caution. Essentially, the “patient” stakeholder group within this report generally encompasses individuals diagnosed with MCI to those with moderate-AD. Thus, to

extrapolate the current findings to patients at the very beginning or very end of the AD spectrum would be erroneous and unrepresentative. Ultimately, this necessitates a closer examination of patients at all points along the disease pathway in order to elucidate the subtle differences in outcome prioritisation across the disease spectrum.

There was also insufficient evidence to provide a comprehensive answer to our second research question, concerning stakeholders' interpretations of a "meaningful delay" in disease progression. This gap in the literature will be explored further in other ROADMAP consortium activities. Similarly, given the small number of included articles which addressed the opinions of healthcare professionals, there is insufficient evidence to draw confident and high quality conclusions regarding this stakeholder group. It is likely that the views of healthcare professionals are more often presented in opinion pieces – which were excluded from our review. Current and future endeavours of the ROADMAP working group also aim to address this gap.

Finally, alongside various quality issues of the included studies identified in Annexe V, it is also important to consider the representativeness of the samples recruited in these studies. Overall, there was a preponderance of white, middle-class participants represented in the studies identified by this review. Thus, it is difficult to ascertain the generalisability of our findings to participants from underrepresented communities. It is possible that the priorities of individuals from underrepresented socio-economic groups would be different. Comparisons by ethnic and cultural differences would not have been accurate or possible in the present review, given a lack of information regarding ethnic groups. Researchers are therefore encouraged to represent disadvantaged or minority groups in future research activities.

4.3. Conclusions

This review summarises those outcomes of AD across the spectrum which are arguably of the greatest importance to patients, caregivers and healthcare professionals implicated in the disease process. Recurring outcomes across all three stakeholder groups, such as memory, patient independence and autonomy, mental health, caregiver burden, health services and disease information and patient quality of life, might be central to medical decision-making and the development of protocols for clinical trials and associated research. It is important to acknowledge that there were discrepancies present between the stakeholder groups. Ultimately the opinions of the patient should be at the forefront of research activities. As there was limited evidence to define a "meaningful delay" in AD disease progression, future research is required to shed light on this important issue.

ANNEXES

Annexe I. Working groups

Develop protocol	Amanda Ly (UEDIN) Anders Gustavsson (ROCHE) Anna Ponjoan (IDIAP JORDI GOL) Catherine Reed (Eli Lilly) Cathie Sudlow (UEDIN) Chi-Hun Kim (UOXF) Chris Edgar (ROCHE)	Christin Bexelius (ROCHE) Christophe Bintener (AE) Claire Tochel (UEDIN) Josep Garre-Olmo (IDIAP JORDI GOL) Julie Chandler (Eli Lilly) Lindsay Lee Lair (JPNV) Michele Potashman (BIOGEN)
Test and run search strategies	Claire Tochel Stephanie Cline (Takeda)	Maike Winters (Roche)
Develop inclusion & exclusion criteria	Alex McKeown (UOXF) Anders Gustavsson Anna Ponjoan Chi-Hun Kim	Claire Tochel Emilse Roncanciodiaz (GE) Josep Garre-Olmo Enrico Fantoni (GE)
Screen titles & abstracts	Alex McKeown Anna Ponjoan Helen Baldwin (UOXF) Michael Smith (UEDIN)	Claire Tochel Emilse Roncanciodiaz Josep Garre-Olmo Enrico Fantoni
Quality appraisal of full-text studies & data extraction	Alex McKeown Claire Tochel Buket Öztürk (AU) Emilse Roncanciodiaz Enrico Fantoni Helen Baldwin	Isabella Friis Jørgensen (UCPH) Josep Garre-Olmo Lars Pedersen (AU) Michael Smith Olin Janssen (UM) Stephanie Voß (UM)
Other	Grey literature	Claire Tochel Christoph Jindra (UOXF)
	Translation	Behnam Esfandiari Jahromi Natalia Monteiro Calanzani Cameron Werner
	Peer review interim and final reports	Anna Ponjoan Catherine Reed Chi-Hun Kim Christophe Bintener Enrico Fantoni Michele Potashman Amanda Ly Mia Nelson (UEDIN) Anders Gustavsson Cathie Sudlow Christin Bexelius

Annexe II. Medline search strategy

Table 4. Medline search strategy with hits

	Search	Terms	Results
delay of disease progression	1	((delay or improv* or alleviat* or treat* or reduc* or lessen or prevent* or shorten or slow) and (symptom* or condition or effect or outcome)).ti,ab.	2,207,579
	2	disease progression/	135,023
	3	"disease progression".ab,ti.	51,644
	4	decline.ab,ti.	152,033
	5	1 or 2 or 3 or 4	2,460,864
patients & carers	6	Patients/	19,264
	7	Caregivers/	29,294
	8	patient*.ti,ab.	5,192,569
	9	(care?giver* or carer*).ti,ab.	49,283
	10	"support worker*".ti,ab.	547
	11	6 or 7 or 8 or 9 or 10	5,230,365
healthcare professionals	12	Allied Health Personnel/	11,059
	13	exp Health Personnel/	452,821
	14	((doctor* or medical or nurs* or physi* or clinic* or geriatric* or psychiatr* or "allied health" or neurolog* or health?care) and (prof* or practitioner)).ti,ab.	395,792
	15	12 or 13 or 14	799,266
AD across the spectrum	16	Alzheimer Disease/	81,153
	17	(alzheimer* adj (disease or dement*)).ti,ab.	94,179
	18	Dementia/	44,079
	19	dementia.ti,ab.	76,284
	20	((pre\$clinical or prodromal or pre?symptomatic) and (alzheimer * or dementia)).ti,ab.	1,621
	21	("mild cognitive impairment" or MCI or A\$MCI or M\$MCI or N\$MCI or CIND).ti,ab.	16,196
	22	pre?senile.ab,ti.	1,342
	23	16 or 17 or 18 or 19 or 20 or 21 or 22	174,946
Outcomes	24	"cost of illness".ab,ti.	1,177
	25	"Quality of Life"/	157,608
	26	("quality of life" or QOL or QALY or HRQOL or (health adj utili*)).ti,ab.	187,855
	27	(econom* and (burden or impact)).ti,ab.	36,107
	28	((cost* or resource) adj utili?ation) or hcru).ti,ab.	6,591
	29	((neuropsychiatr* or psychiatr* or behavi*) and symptom*).ti,ab.	94,932
	30	"dependency (psychology)"/	2,442
	31	dependen*.ab,ti.	1,329,162
	32	Health Resources/	11,033
	33	exp "Costs and Cost Analysis"/	213,357
	34	cost.ab,ti.	282,561

	35	diagnosis/ or early diagnosis/ or prodromal symptoms/	40,189
	36	(cognit* or memory or function* or depress* or anxiety or well?being or language or communicat*).ab,ti.	3,492,288
	37	(caregiver and (burden or impact)).ab,ti.	5,274
	38	"Activities of Daily Living"/	59,056
	39	activities of daily living.ab,ti.	18,269
	40	(caregiver and (burden or impact or stress or time)).ab,ti.	8,163
	41	outcome.ab,ti.	722,615
	42	Biomarkers/ or Amyloid/ or tau Proteins/	242,077
	43	(tau or biomarker or amyloid).ab,ti.	146,849
	44	24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35 or 36 or 37 or 38 or 39 or 40 or 41 or 42 or 43	5,734,100
Priorities	45	Health Priorities/	10,275
	46	(priorit* or importan* or valued or valuable or critical or wish or rank or relevan* or preferen* or meaningful).ti.	243,098
	47	45 or 46	250,069
Study method	48	(qualitative or delphi or "nominal group" or "priority setting" or "mixed method*" or multi?method or "patient?centred" or poll or consensus or "interpretive phenomenological analysis" or "thematic analysis" or "grounded theory" or "content analysis" or discours* or "lived experience*" or phenomenolog* or "conjoint analysis").ab,ti.	308,349
	49	"surveys and questionnaires"/ or delphi technique/ or health surveys/ or interviews as topic/ or focus groups/ or narration/ or qualitative research/	517,189
	50	((("semi-structured" or semistructured or unstructured or informal or "in-depth" or indepth or "face-to-face" or structured or guide) adj3 (interview* or discussion* or questionnaire* or survey*)) or (focus group* or qualitative or ethnograph* or fieldwork or "field work" or "key informant")).ti,ab.	226,399
	51	Humans/	17,026,907
	52	(48 or 49 or 50) and 51	724,698
	53	(23 and 11 and 44 and 47 and 52) or (23 and 15 and 44 and 47 and 52) or (23 and 11 and 5 and 52) or (23 and 15 and 5 and 52)	1,705

The final row above shows the grouped terms combined as indicated in table 1 in chapter 2 to answer each research question.

- Research question 1
 - patients and carers: 23 and 11 and 44 and 47 and 52
 - healthcare professionals: 23 and 15 and 44 and 47 and 52
- Research question 2
 - patients and carers: 23 and 11 and 5 and 52
 - healthcare professionals: 23 and 15 and 5 and 52

Annexe III. Comparable search strategies for other databases

Table 5. Embase search strategy

Set	Search Statement
1	Alzheimer Disease/
2	(alzheimer* adj (disease or dement*)).ti,ab.
3	Dementia/
4	dementia.ti,ab.
5	((pre\$clinical or prodromal or pre?symptomatic) and (alzheimer* or dementia)).ti,ab.
6	("mild cognitive impairment" or MCI or A\$MCI or M\$MCI or N\$MCI or CIND).ti,ab.
7	pre?senile.ab,ti.
8	1 or 2 or 3 or 4 or 5 or 6 or 7
9	Patient/
10	Caregiver/
11	patient*.ti,ab.
12	(care?giver* or carer*).ti,ab.
13	support worker*.ti,ab.
14	9 or 10 or 11 or 12 or 13
15	paramedical personnel/
16	exp health care personnel/
17	((doctor* or medical or nurs* or physi* or clinic* or geriatric* or psychiatr* or "allied health" or neurolog* or health?care) and (prof* or practitioner)).ti,ab.
18	15 or 16 or 17
19	cost of illness.ab,ti.
20	quality of life/
21	("quality of life" or QOL or QALY or HRQOL or (health adj utili*)).ti,ab.
22	(econom* and (burden or impact)).ti,ab.
23	((cost* or resource) adj utili?ation) or hcr).ti,ab.
24	((neuropsychiatr* or psychiatr* or behavi*) and symptom*).ti,ab.
25	dependency (psychology)/
26	dependen*.ab,ti.
27	health care planning/
28	cost/ or "cost benefit analysis"/
29	cost.ab,ti.
30	diagnosis/ or "early diagnosis"/ or "prodromal symptom"/
31	(cognit* or memory or function* or depress* or anxiety or well?being or language or communicat*).ab,ti.
32	(caregiver and (burden or impact)).ab,ti.
33	daily life activity/
34	activities of daily living.ab,ti.
35	(caregiver and (burden or impact or stress or time)).ab,ti.

36	outcome.ab,ti.
37	biological markers/ or "amyloid"/ or "amyloid A protein"/ or "amyloid beta protein"/ or "tau Protein"/
38	(tau or biomarker or amyloid).ab,ti.
39	19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35 or 36 or 37 or 38
40	health care planning/
41	(priorit* or importan* or valued or valuable or critical or wish or rank or relevan* or preferen* or meaningful).ti.
42	40 or 41
43	(qualitative or delphi or "nominal group" or "priority setting" or "mixed method*" or multi?method or "patient?centred" or poll or consensus or "interpretive phenomenological analysis" or "thematic analysis" or "grounded theory" or "content analysis" or discours* or "lived experience*" or phenomenolog* or "conjoint analysis").ab,ti.
44	health care survey/ or "questionnaires"/ or "health survey"/ or "Delphi study"/ or "interview"/ or "information processing"/ or "narrative"/ or "qualitative research"/
45	((("semi-structured" or semistructured or unstructured or informal or "in-depth" or indepth or "face-to-face" or structured or guide) adj3 (interview* or discussion* or questionnaire* or survey*)) or (focus group* or qualitative or ethnograph* or fieldwork or "field work" or "key informant")).ti,ab.
46	human/
47	(43 or 44 or 45) and 46
48	((delay or improv* or alleviat* or treat* or reduc* or lessen or prevent* or shorten or slow) and (symptom* or condition or effect or outcome)).ti,ab.
49	disease course/
50	disease progression.ab,ti.
51	decline.ab,ti.
52	48 or 49 or 50 or 51
53	8 and 14 and 39 and 42 and 47
54	8 and 18 and 39 and 42 and 47
55	8 and 14 and 47 and 52
56	8 and 18 and 47 and 52
57	53 or 54 or 55 or 56

Table 6. Cinahl search strategy

#	Query
S1	Alzheimer's Disease/ OR (TI (alzheimer* N1 (disease or dement*)) or AB (alzheimer* N1 (disease or dement*))) OR Dementia/ OR dementia.ti,ab. OR (TI ((pre\$clinical or prodromal or pre?symptomatic) and (alzheimer * or dementia)) or AB ((pre\$clinical or prodromal or pre?symptomatic) and (alzheimer * or dementia))) OR (("mild cognitive impairment" or MCI or A\$MCI or M\$MCI or N\$MCI or CIND) or AB ("mild cognitive impairment" or MCI or A\$MCI or M\$MCI or N\$MCI or CIND)) OR (TI pre#senile or AB pre#senile)
S2	Patients/ OR Caregivers/ OR (TI patient* or AB patient*) OR (TI (care?giver* or carer*) or AB (care?giver* or carer*)) OR (TI "support worker*" or AB "support worker*")
S3	Allied Health Personnel/ OR exp Health Personnel/ OR (TI ((doctor* or medical or nurs* or physi* or clinic* or geriatric* or psychiatr* or "allied health" or neurolog* or health?care) and (prof* or practitioner)) or AB ((doctor* or medical or nurs* or physi* or clinic* or geriatric* or psychiatr* or "allied health" or neurolog* or health?care) and (prof* or practitioner)))
S4	"Economic Aspects of Illness"/ OR "Quality of Life"/ OR (TI "quality of life" or QOL or QALY or HRQOL or (health adj utili*)) or AB "quality of life" or QOL or QALY or HRQOL or (health adj utili*)) OR (TI (econom* and (burden or impact)) or AB (econom* and (burden or impact))) OR (TI (((cost* or resource) N1 utili?ation) or hcru) or AB (((cost* or resource) N1 utili?ation) or hcru)) OR (TI ((neuropsychiatr* or psychiatr* or behavi*) and symptom*) or AB ((neuropsychiatr* or psychiatr* or behavi*) and symptom*)) OR "dependency (psychology)"/ OR (TI dependen* or AB dependen*) OR Health Resource Utilization/ OR ("Costs and Cost Analysis"/) OR cost.ab,ti. OR (diagnosis/ or early diagnosis/)
S5	(AB (cognit* or memory or function* or depress* or anxiety or well?being or language or communicat*) or TI (cognit* or memory or function* or depress* or anxiety or well?being or language or communicat*)) OR (TI (caregiver and (burden or impact)) or AB (caregiver and (burden or impact))) OR "Activities of Daily Living"/ OR (TI activities of daily living OR AB activities of daily living) OR (TI (caregiver and (burden or impact or stress or time)) or AB (caregiver and (burden or impact or stress or time))) OR (TI outcome OR AB outcome) OR (Biological markers/ or Amyloid neuropathies/) OR (TI (tau or biomarker or amyloid) or AB (tau or biomarker or amyloid))
S6	S4 OR S5
S7	(Health Services Needs and Demand/) OR (TI (priorit* or importan* or valued or valuable or critical or wish or rank or relevan* or preferen* or meaningful))

S8	(TI (qualitative or delphi or "nominal group" or "priority setting" or "mixed method*" or multi?method or "patient?centred" or poll or consensus or "interpretive phenomenological analysis" or "thematic analysis" or "grounded theory" or "content analysis" or discours* or "lived experience*" or phenomenolog* or "conjoint analysis") or AB (qualitative or delphi or "nominal group" or "priority setting" or "mixed method*" or multi?method or "patient?centred" or poll or consensus or "interpretive phenomenological analysis" or "thematic analysis" or "grounded theory" or "content analysis" or discours* or "lived experience*" or phenomenolog* or "conjoint analysis")) OR ("surveys and questionnaires"/ or delphi technique/ or surveys/ or interviews/ or focus groups/ or narratives/ or qualitative studies/) OR (TI (((("semi-structured" or semistructured or unstructured or informal or "in-depth" or indepth or "face-to-face" or structured or guide) adj3 (interview* or discussion* or questionnaire* or survey*)) or (focus group* or qualitative or ethnograph* or fieldwork or "field work" or "key informant"))) or AB (((("semi-structured" or semistructured or unstructured or informal or "in-depth" or indepth or "face-to-face" or structured or guide) adj3 (interview* or discussion* or questionnaire* or survey*)) or (focus group* or qualitative or ethnograph* or fieldwork or "field work" or "key informant")))) AND Human/
S9	(TI ((delay or improv* or alleviat* or treat* or reduc* or lessen or prevent* or shorten or slow) and (symptom* or condition or effect or outcome)) or AB ((delay or improv* or alleviat* or treat* or reduc* or lessen or prevent* or shorten or slow) and (symptom* or condition or effect or outcome))) OR disease progression/ OR (TI "disease progression" or AB "disease progression") OR (TI decline or AB decline)
S10	S1 AND S2 AND S6 AND S7 AND S8
S11	S1 AND S3 AND S6 AND S7 AND S8
S12	S1 AND S2 AND S8 AND S9
S13	S1 AND S3 AND S8 AND S9
S14	S10 OR S11 OR S12 OR S13

Table 7. *PsycInfo search strategy*

Set	Search Statement
1	Alzheimer Disease/
2	(alzheimer* adj (disease or dement*)).ti,ab.
3	Dementia/
4	dementia.ti,ab.
5	((pre\$clinical or prodromal or pre?symptomatic) and (alzheimer * or dementia)).ti,ab.
6	("mild cognitive impairment" or MCI or A\$MCI or M\$MCI or N\$MCI or CIND).ti,ab.
7	pre?senile.ab,ti.
8	1 or 2 or 3 or 4 or 5 or 6 or 7
9	Patients/
10	Caregivers/
11	patient*.ti,ab.
12	(care?giver* or carer*).ti,ab.
13	"support worker*".ti,ab.

14	9 or 10 or 11 or 12 or 13
15	Allied Health Personnel/
16	exp Health Personnel/
17	((doctor* or medical or nurs* or physi* or clinic* or geriatric* or psychiatr* or "allied health" or neurolog* or health?care) and (prof* or practitioner)).ti,ab.
18	15 or 16 or 17
19	"cost of illness".ab,ti.
20	"Quality of Life"/
21	("quality of life" or QOL or QALY or HRQOL or (health adj utili*)).ti,ab.
22	(econom* and (burden or impact)).ti,ab.
23	((cost* or resource) adj utili?ation) or hcru).ti,ab.
24	((neuropsychiatr* or psychiatr* or behavi*) and symptom*).ti,ab.
25	"dependency (personality)"/
26	dependen*.ab,ti.
27	"Health Care Costs"/
28	exp "Costs and Cost Analysis"/
29	cost.ab,ti.
30	diagnosis/ or early diagnosis/ or prodromal symptoms/
31	(cognit* or memory or function* or depress* or anxiety or well?being or language or communicat*).ab,ti.
32	(caregiver and (burden or impact)).ab,ti.
33	"Activities of Daily Living"/
34	activities of daily living.ab,ti.
35	(caregiver and (burden or impact or stress or time)).ab,ti.
36	outcome.ab,ti.
37	Biomarkers/ or Amyloid/ or tau Proteins/
38	(tau or biomarker or amyloid).ab,ti.
39	19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35 or 36 or 37 or 38
40	Health Attitudes/
41	(priorit* or importan* or valued or valuable or critical or wish or rank or relevan* or preferen* or meaningful).ti.
42	40 or 41
43	(qualitative or delphi or "nominal group" or "priority setting" or "mixed method*" or multi?method or "patient?centred" or poll or consensus or "interpretive phenomenological analysis" or "thematic analysis" or "grounded theory" or "content analysis" or discours* or "lived experience*" or phenomenolog* or "conjoint analysis").ab,ti.
44	"surveys and questionnaires"/ or delphi technique/ or health surveys/ or interviews as topic/ or focus groups/ or narration/ or qualitative research/
45	((("semi-structured" or semistructured or unstructured or informal or "in-depth" or indepth or "face-to-face" or structured or guide) adj3 (interview* or discussion* or questionnaire* or survey*)) or (focus group* or qualitative or ethnograph* or fieldwork or "field work" or "key informant")).ti,ab.

46	43 or 44 or 45
47	limit 46 to human
48	((delay or improv* or alleviat* or treat* or reduc* or lessen or prevent* or shorten or slow) and (symptom* or condition or effect or outcome)).ti,ab.
49	disease course/
50	"disease progression".ab,ti.
51	decline.ab,ti.
52	48 or 49 or 50 or 51
53	(8 and 14 and 39 and 42 and 47) or (8 and 18 and 39 and 42 and 47) or (8 and 14 and 52 and 47) or (8 and 18 and 52 and 47)

Table 8. CRD search strategy

Item	Search terms in CRD database
1	(Alzheimer Disease) IN DARE, NHSEED, HTA
2	((alzheim* ADJ (disease OR dement*)):ti,ab) IN DARE, NHSEED, HTA
3	(Dementia) IN DARE, NHSEED, HTA
4	(dementia:ti,ab) IN DARE, NHSEED, HTA
5	((pre-clinical OR preclinical OR prodromal OR pre-symptomatic OR presymptomatic) AND (alzheim* OR dementia)):ti,ab) IN DARE, NHSEED, HTA
6	((mild cognitive impairment OR MCI OR AMCI OR MMCI OR NMCI OR CIND):ti,ab) IN DARE, NHSEED, HTA
7	((pre-senile OR presenile):ti,ab) IN DARE, NHSEED, HTA
8	#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7
9	((cost of illness):ti,ab) IN DARE, NHSEED, HTA
10	(quality of life) IN DARE, NHSEED, HTA
11	((quality of life OR QOL OR QALY OR HRQOL OR (health ADJ utili*)):ti,ab) IN DARE, NHSEED, HTA
12	((econom* AND (burden OR impact)):ti,ab) IN DARE, NHSEED, HTA
13	((cost* OR resource) ADJ utilization) OR hcru):ti,ab) IN DARE, NHSEED, HTA
14	((neuropsychiatr* OR psychiatr* OR behavi*) AND symptom*):ti,ab) IN DARE, NHSEED, HTA
15	(dependency AND psychology) IN DARE, NHSEED, HTA
16	(dependen*:ti,ab) IN DARE, NHSEED, HTA
17	(Health Resources) IN DARE, NHSEED, HTA
18	(exp costs and cost analysis) IN DARE, NHSEED, HTA
19	(cost:ti,ab) IN DARE, NHSEED, HTA
20	(diagnosis OR early diagnosis OR prodromal symptoms) IN DARE, NHSEED, HTA

21	((cognit* OR memory OR function* Or depress* OR anxiety OR well-being OR wellbeing OR language OR communicat*):ti,ab) IN DARE, NHSEED, HTA
22	((caregiver AND (burden OR impact)):ti,ab) IN DARE, NHSEED, HTA
23	(activities of daily living) IN DARE, NHSEED, HTA
24	((activities of daily living):ti,ab) IN DARE, NHSEED, HTA
25	((caregiver AND (burden OR impact OR stress OR time)):ti,ab) IN DARE, NHSEED, HTA
26	(outcome:ti,ab) IN DARE, NHSEED, HTA
27	(biomarkers OR amyloid OR tau proteins) IN DARE, NHSEED, HTA
28	((tau OR biomarker OR amyloid):ti,ab) IN DARE, NHSEED, HTA
29	#9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25 OR #26 OR #27 OR #28 OR #29

Annexe IV. Grey literature search strategy & results

Purpose: to seek evidence which answers our research questions from sources not captured by the main SLR searching process.

Goal: to demonstrate reasonable attempts to find information from organisations across Europe which represent, support or otherwise engage with people with AD. If they have undertaken qualitative research, interviews or focus groups with people with AD or their carers / supporters which answer our questions we want to try and find it – this may be available directly on their website or they may have a list of titles available on request by email. We will also include google which has a very broad reach for such documents.

Scope: although such reports are a different type of evidence (i.e. they are unlikely to be formal research studies) they still must be relevant to our research questions and meet our inclusion criteria. As it is impractical to achieve a comprehensive search given the number of potential sources, the goal is to demonstrate a systematic approach and reasonable effort to look for information in as unbiased a way as possible.

Process

1. Identify a range of relevant websites including generic grey literature sources, condition-specific organisations & generic search engines.
2. Where the site has a search facility use broad search terms below, otherwise scan report names for relevance to the research questions
 - a. “Alzheimer” and “outcome”
 - b. “Alzheimer” and “progression”
3. Where possible use the search to apply date limits or check for date before downloading
 - a. 2008 – 2017
4. Save details of all searches in the table below, no of hits, relevant report titles, efforts made to acquire full text.
5. On acquisition of full text report, read it and check whether it provides evidence to answer either of the research questions, and if so, save it and log citation details.
6. Read relevant full reports, extract useful information and synthesise.

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Table 9. Summary of results

Date	Source	Search terms	Hits	details
06/09/2017	http://www.greylit.org	Alzheimer & outcome 2008 - 2017	0	
		Alzheimer & progression 2008 - 2017	1	2014-2015 Alzheimer's disease progress report : advancing research toward a cure, Rodgers, Anne Brown, National Institute on Aging – broken link on website – see follow up below
26/10/2017	http://www.greylit.org	Alzheimer + outcome 2008 - 2017	0	
26/10/2017	http://www.greylit.org	Alzheimer + outcome	9	<p>2014-2015 Alzheimer's disease progress report : advancing research toward a cure, Rodgers, Anne Brown, National Institute on Aging (http://www.questri.com/wp-content/uploads/2016/09/2014-2015_alzheimers-disease-progress-report.pdf)</p> <ul style="list-style-type: none"> Only section CATEGORY E. CARE AND CAREGIVER SUPPORT was potentially interesting. However, the section did neither discuss which outcomes should be prioritised, nor did it discuss meaningful delay. The report is thus not of further interest
26/10/2017	http://www.greylit.org	Alzheimer + progression 2008 - 2017	3	None relevant

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Date	Source	Search terms	Hits	details
26/10/2017	http://www.greylit.org	Alzheimer + progression (year was taken into account manually)	52	<p>ALZHEIMER'S DISEASE CAREGIVING ADVISORY GROUP - Convened by the National Alliance for Caregiving (http://www.caregiving.org/data/AlzhADPilotCaregiverAdBrd.pdf)</p> <ul style="list-style-type: none"> While the report has a section on how to involve caregivers in research so that guidelines can include evidence that reflects the caregiving experience, the report does not go beyond the recommendation of doing so and does not provide evidence on priorities from family caregivers or discusses meaningful delay <p>National Plan to Address Alzheimer's Disease: 2013 Update (https://aspe.hhs.gov/system/files/pdf/102516/NatlPlan2013.pdf)</p> <ul style="list-style-type: none"> Item "Action 2.D.2: Identify and review measures of high-quality dementia care" is aimed at identifying measures for high-quality measures care and emphasises consensus. However, it is a goal and project, thus no further information can be found in the report.
06/09/2017	https://www.nia.nih.gov/ National Institute on Aging (follow up from above as broken link to this document)	Email to National Institute on Aging	0	Response from NIAIC (7 th Sep): <i>"Unfortunately, the "2014-2015 Alzheimer's Disease Progress Report: Advancing Research Toward a Cure" is no longer available on our website."</i>
	Comment on above			Available online see link above
06/09/2017	http://www.opengrey.eu	Alzheimer & outcome 2008 - 2017	3	All theses - excluded
		Alzheimer & progression 2008 - 2017	53	All theses - excluded
26/10/2017	http://www.opengrey.eu	Alzheimer & outcome 2008 - 2017	0	
26/10/2017	http://www.opengrey.eu	Alzheimer & outcome	9	All theses - excluded
26/10/2017	http://www.opengrey.eu	Alzheimer & progression 2008 - 2017	0	

Date	Source	Search terms	Hits	details
26/10/2017	http://www.opengrey.eu	Alzheimer & progression	53	All theses - excluded
06/09/2017	http://explore.bl.uk British library	Alzheimer & outcome 2008 - 2017	13 books 6 theses 3 audio recordings	Lay perspectives of medicines for dementia: a qualitative study Taylor, Denise Ann, University of Bath 2009 – thesis but relevant for elsewhere in WP2?
		Alzheimer & progression 2008 - 2017	20 theses 17 books 6 audio recordings	None answer review questions
26/10/2017	http://explore.bl.uk British library	Alzheimer & outcome (restricted to start and end date)	23, 3 audio 6 theses 14 books	<i>Taylor, D. A., 2009. Lay Perspectives of Medicines for Dementia: a Qualitative Study. Thesis (Doctor of Philosophy (PhD)). University of Bath as above</i> Intellectual disability and dementia : research into practice / edited by Karen Watchman ; foreword by Diana Kerr. London : Jessica Kingsley Publishers, 2014. <i>Not grey literature.</i>
26/10/2017	http://explore.bl.uk British library	Alzheimer & progression (restricted to start and end date)	43, 20 theses 17 books 6 audio	MacQuarrie, C. R. (2008). Mid-Life Transitions: Spousal Experiences of Coping with Dementia of the Alzheimer Type. In H. S. Jeong (Ed.), Alzheimer's Disease in the Middle-Aged (pp. 225-253). New York: Nova Science Publishers, Inc. <i>Not grey literature.</i>
06/09/2017	http://www.alzscot.org	Alzheimer & outcome 2008 - 2017	35	Perspectives on outcomes for early stage support See below
26/10/2017	http://www.alzscot.org	Alzheimer & outcome	36	Perspectives on outcomes for early stage support <i>Trying to retrieve the site on 30.10.2017 lead to "Page not found error". I made an inquiry (info@alzscot.org). No reply 1.11.2017</i>
26/10/2017	http://www.alzscot.org	Alzheimer & outcome 2008 - 2017	1	Scotland's National Dementia Strategy 2017-2020 <ul style="list-style-type: none"> Is a strategy paper and as such does not address outcome priorities beyond those being decided upon in some, non-disclosed way

Date	Source	Search terms	Hits	details
26/10/2017	http://www.alzscot.org	Alzheimer & progression 2008 - 2017	1	Scotland's National Dementia Strategy 2017-2020 Is a strategy paper and as such does not address outcome priorities beyond those being decided upon in some, non-disclosed way
26/10/2017	http://www.alzscot.org	Alzheimer + progression	56	National Dementia Dialogue events 2015 <i>Only events, but results would be interesting. I got in touch with Alzheimer Scotland (info@alzscot.org) and made an inquiry whether results are published somewhere. No reply by 1.11.2017</i>
06/09/2017	gcolston@alzscot.org email to request info related to Practitioner Research Older People programme		0	Response from Lindsay Kinnaird (25 th Sep): "To my knowledge none of the projects would contribute to the questions below".

06/09/2017	https://www.google.co.uk	Alzheimer & outcome 2008 - 2017	<p>Outcomes from the James Lind Alliance priority setting partnership – 2013</p> <ul style="list-style-type: none"> • Brought together a wide range of organisations that collectively represent the views of people affected by dementia, practitioners and clinicians to try to agree on priorities regarding the care, treatment, diagnosis and prevention of dementia → result is list of top 10 priorities for research • The report discusses questions that were submitted via a questionnaire. While these questions can be interpreted as giving evidence of what seems important to carers and other stakeholders, it is not the main focus of the report and thus, without making the step to organise the information into priorities, the report cannot answer questions of the systematic review. <ul style="list-style-type: none"> ◦ Also independence made it on top 1 question • They also only refer to dementia really, not AD <p>Consultation on Commissioning Outcomes Framework February 2012</p> <ul style="list-style-type: none"> • The report is a response to the Commissioning Outcomes Framework which seems to be an initiative that tries to find indicators for outcome measures for people dementia across the health and social care system. As such, it proposes indicators that measure outcomes at an aggregate level but does not provide evidence beyond that on priorities of outcomes by patients, carer or healthcare professionals. It mentions quality of life but as the abstract fuzzy concept <p>Outcomes measures in a decade of dementia and mild cognitive impairment trials – Harrison, 2016 (already included in main search)</p> <p>Priority of Treatment Outcomes for Caregivers and Patients with Mild Cognitive Impairment: Preliminary Analyses, Gonzalez-Barrios, 2016 (already included in main search)</p> <p>Outcomes Assessment in Clinical Trials of Alzheimer's Disease and its Precursors: Ready for Short-term and Long-term Clinical Trial Needs <i>Not grey literature (see below)</i></p> <p>Scotland's National Dementia Strategy 2017-2020</p>
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Date	Source	Search terms	Hits	details
				<ul style="list-style-type: none"> Is a strategy paper and as such does not address outcome priorities beyond those being decided upon in some, non-disclosed way <p>Beyond barriers. Developing a palliative care approach for people in the later stages of dementia. An Alzheimer Scotland Partnership Project – 2010?</p> <ul style="list-style-type: none"> Objective of the “Beyond barriers” project were the development, implementation and evaluation of an educational programme that focusses on communication, to provide relatives with an equal opportunity to participate in the programme, to enable staff to fully participate, to enable care home staff and relative to influence the practice of other staff within their care home and so on. The project didn’t try to elicit information on patient priorities or meaningful delays and is thus nor relevant <p>Dementia outcome measures: charting new territory. Report of a JPND working group on longitudinal cohorts, 2015 (http://www.neurodegenerationresearch.eu/)</p> <ul style="list-style-type: none"> Study involves experts to identify the best dementia outcome measures. Report does not distinguish between types of dementia It is more a review and ranking of diagnostic and measurement instruments <p>World Alzheimer Report 2016 Improving healthcare for people living with dementia coverage, Quality and costs now and in the future</p> <ul style="list-style-type: none"> Mentions importance of eliciting individual preferences but seems to not handle the issue themselves and thus does not answer the research question

26/10/2017	Google.com	Alzheimer & outcome 2008 - 2017	2,690,000 only first 10 pages checked	<p>2011 Alzheimer Europe Survey: The Value of Knowing (http://www.alzheimer-europe.org/Research/Value-of-Knowing)</p> <ul style="list-style-type: none"> I went over the questionnaire and the questions are all related to knowledge about AD or whether or not somebody would want use a diagnostic tool to learn about the likelihood of a future diagnosis. The research does not contribute to answering the review question <p>Who cares? The state of dementia care in Europe (http://www.alzheimer-europe.org/Publications/Alzheimer-Europe-Reports)</p> <ul style="list-style-type: none"> Reports results of survey of people caring for AD patients. There is one question that asks for the most problematic symptoms but that's about it <p>Rotpacki et al 2017: Clinically Meaningful Outcomes in Early Alzheimer Disease - A Consortia-Driven Approach to Identifying What Matters to Patients. Therapeutic Innovation & Regulatory Science 51(3). <i>Not grey literature.</i></p> <p>Dementia 2012: A national challenge (https://www.alzheimers.org.uk/download/downloads/id/1389/alzheimers_society_dementia_2012- full_report.pdf)</p> <ul style="list-style-type: none"> Does not itself prioritise outcomes but instead uses those from Dementia Action Alliance National Dementia Declaration, which seems to be participatory. It thus uses priorities defined elsewhere and does not elicit information themselves. One should however look at the report they are citing <p>Women and Dementia A Global Challenge (https://www.gadaalliance.org/wp-content/uploads/2017/02/Women-Dementia-A-Global-Challenge_GADAA.pdf)</p> <ul style="list-style-type: none"> This report provides a brief overview of the key dementia-related issues facing women around the globe, highlighting more comprehensive literature on the subject. It then considers the next steps urgently needed to address these challenges. It identifies where national dementia strategies have begun to take gender perspectives; and analyses which international policy frameworks must be used to construct gendersensitive responses. The time is now for gender-equality advocates and those
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Date	Source	Search terms	Hits	details
				<p>involved in dementia policy and practice to put women at the front and centre of global dementia action</p> <ul style="list-style-type: none"> It is a systematic review and thus does not explicitly elicit information on outcomes that are not included via the publications it includes. It also focuses on national dementia plans and strategies <p>Sorensen et al 2008: Early counselling and support for patients with mild Alzheimer's disease and their caregivers: A qualitative study on outcome. Aging and Mental Health 2008 12(4) <i>Not grey literature.</i></p> <p>Harisson et al 2016: Outcomes measures in a decade of dementia and mild cognitive impairment trials. Alzheimer's Research & Therapy 2016 8:48. <i>Not grey literature.</i></p> <p>Posner et al 2017: Outcomes Assessment in Clinical Trials of Alzheimer's Disease and its Precursors: Ready for Short-term and Long-term Clinical Trial Needs. Innovations in Clinical Neuroscience 14(1-2) <i>Not grey literature.</i></p>
26/10/2017	Google.com	Alzheimer & progression 2008 - 2017	9,450,000, only first 10 pages checked	None answer review questions
26/10/2017	https://www.alzheimers.org.uk	Alzheimer & outcome 2008 - 2017	3	None answer review questions
26/10/2017	https://www.alzheimers.org.uk	Alzheimer & progression 2008 - 2017	6	<p>End of life care (https://www.alzheimers.org.uk/info/20091/position_statements/139/end_of_life_care)</p> <ul style="list-style-type: none"> Mentions some relevant outcomes, however, it is not a systematic report but just a piece on the website and does not itself elicit the information but, if at all, quotes other publications

Date	Source	Search terms	Hits	details
30/10/2017	http://www.alzheimer-europe.org/Research	Alzheimer & outcome 2008 - 2017	910	<p><i>Only first 10 result page were screened and only first few paragraphs were screened to assess suitability</i></p> <p>Working group explores views of people with dementia and carers about outcome measures (http://www.alzheimer-europe.org/News/EU-developments/Wednesday-24-June-2015-Working-group-explores-views-of-people-with-dementia-and-carers-about-outcome-measures/(language)/eng-GB)</p> <ul style="list-style-type: none"> • Not itself a report but just a brief news story
30/10/2017	http://www.alzheimer-europe.org/Research	Alzheimer & progression 2008 - 2017	1247	<p><i>Only first 10 result page were screened and only first few paragraphs were screened to assess suitability</i></p> <p>None answer review questions</p>
01/11/2017	https://www.base-search.net/	Alzheimer & outcome 2008 - 2017	29	None answer review questions
01/11/2017	https://www.base-search.net/	Alzheimer & progression 2008 - 2017	51	<p>Caring for elders with Alzheimer's disease: experiences of family caregivers</p> <ul style="list-style-type: none"> • Link https://www.revistas.ufg.br/fen/article/view/46488 could not be accessed from my website and I couldn't find anything else on it <p>Olivetti, L et al 2017 Better Journeys for People with Dementia in Northern Sydney. International Journal of Integrated Care, 17(3): A116, pp. 1-8, DOI: dx.doi.org/10.5334/ijic.3228</p> <p><i>Not grey literature (but also only two pages with not much information)</i></p>
01/11/2017	http://copac.jisc.ac.uk/search/form/main	Alzheimer & outcome (year had to be taken out, search in title field)	4	None answer review questions

Date	Source	Search terms	Hits	details
01/11/2017	http://copac.jisc.ac.uk/search/form/main	Alzheimer & progression (year had to be taken out, search in title field)	16	None answer review questions
01/11/2017	https://www.nice.org.uk/About/What-we-do/Evidence-Services/Evidence-Search	Alzheimer & outcome 2008 - 2017	0	
01/11/2017	https://www.nice.org.uk/About/What-we-do/Evidence-Services/Evidence-Search	Alzheimer & progression 2008 - 2017	0	
01/11/2017	https://scholar.google.com/schhp?hl=en&as_sdt=0,5	Alzheimer & outcome 2008 - 2017	82900 only first 10 pages checked	All published results and none seems to answer research questions
01/11/2017	https://scholar.google.com/schhp?hl=en&as_sdt=0,5	Alzheimer & progression 2008 - 2017	135,000 only first 10 pages checked	All published results and none seems to answer research questions

Annexe V. Study characteristics table

Table 10. Study characteristics for research question 1: Priority Outcomes

Author / Location	Participant Demographics	Data Collection Method	Details of Prioritising Outcomes	Reported Outcomes	Risks of Bias / Limitations
Andersen et al. (2008), Canada (English)	N = 27 <u>AD Patients:</u> n=4 females, aged 65+, early-stage AD <u>AD Caregivers:</u> n=4, 1 spouse, 2 adult children, 1 companion <u>AD HPs:</u> n=11, 3 physicians, 4 nurses, 4 pharmacists	Semi-structured interviews, 30-60 minutes, analytic induction applied	Priority inferred: Outcomes related to expectations of cholinesterase inhibitors: As these are <i>expectations regarding treatment</i> , one can assume that these hold importance / priority for the stakeholder groups.	<u>AD Patients:</u> Memory/slowing of forgetfulness, general cognitive health <u>AD Caregivers:</u> Stability of symptoms and general symptom control <u>AD HPs:</u> Stability of symptoms and general symptom control, delaying entry into care, patient social engagement, stability of symptoms and general symptom control, patient QoL, ADL, apathy	<u>CASP:</u> Researchers' own roles regarding bias not assessed <u>Other:</u> Sample size for each stakeholder group is small; outcomes cannot be split for caregiver subgroups (i.e. spouse/child carers); outcome priority is inferred
Barrios et al. (2016), USA (English)	N = 65 <u>MCI Patients:</u> n=16 patients in Study 2, mean age=77.3 (7.1) <u>MCI Caregivers:</u> n=33 in Study 1, mean age=71, 29 spouses, 4 adult children; n=16 in Study 2, mean age=73.1(7.5), 15 spouses/partners, 2 friends.	Participants were measured on 12 outcome scales throughout an intervention: In Study 1, caregivers ranked the outcomes for importance from 1 (most important) to 12 (least important): In Study 2, rankings were compared for patients and caregivers before and after the intervention	Priority explicitly ranked: 12 outcomes: <i>Patient</i> depression, QoL, self-efficacy, anxiety, daily functioning, memory based ADL and distressing behaviours; <i>Caregiver</i> burden, self-efficacy, anxiety, depression and QoL	<u>MCI Patients:</u> Prior to the intervention, MCI patients ranked patient depression as significantly less important (mean rank 7.9) than the MCI patients (mean rank 4.2; p<0.01) <u>MCI Caregivers:</u> ADL, patient self-efficacy, patient mental health, caregiver QoL, patient QoL; <i>Note:</i> caregiver burden and caregiver depression were ranked as the outcomes with <i>least</i> priority by the caregivers	<u>NIH:</u> Sample size justification, power description, effect sizes not provided; ranking method lacking validity and reliability <u>Other:</u> Small sample for survey work; outcomes cannot be compared to one another to determine how they relate; ranking relies on pre-determined set of outcomes; Outcomes cannot be split for caregiver subgroups (i.e. spousal vs child carers)
Beard et al. (2009), USA (English)	N = 85 <u>MCI/AD Patients:</u> n=17 had either mild-AD or MCI aged 65+	14 focus groups conducted throughout the USA, using a common interview guide:	Priority inferred: Data coded for themes using rigorous grounded theory approach	<u>MCI/AD Patients:</u> Patient mental health, patient independence and autonomy, patient	<u>CASP:</u> Recruitment strategy unclear, researchers' own roles regarding bias not assessed

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	<u>MCI/AD Caregivers</u> : n=68 “family support persons”; Aged 35+	Grounded theory applied to analysis.	until data saturation occurred: Hence, themes and reported outcomes were judged to be important	social engagement, patient physical health and mobility, judgement and insight <u>MCI/AD Caregivers</u> : Patient independence and autonomy, memory/slowing of forgetfulness	<u>Other</u> : High dropout rates; outcome priority is inferred; Participant results cannot be split based on subgroups (i.e. AD vs MCI, spousal vs child carers)
Blieszner and Roberto (2010), USA (English)	N = 86 <u>MCI Caregivers</u> : Aged 25-89, 65 were spouses, 15 were adult children, 6 were siblings/other relatives/friends	Individual, face-to-face interviews, participants responded to 12 open ended questions relating to various outcomes and the caregiving experience: Transcripts analysed thematically	Priority inferred : Data coded for themes using rigorous open coding, thematic approach: Transferability discussed with reference to previous research: Hence, themes and reported outcomes were judged to be important	<u>MCI Caregivers</u> : Patient apathy, patient sleep patterns, caregiver burden, quality of patient-caregiver relationship, family participation in care, health services and disease information	<u>CASP</u> : Researchers’ own roles regarding bias not assessed <u>Other</u> : Outcome priority is inferred; Participant results cannot be split based on subgroups (i.e. spousal vs child carers)
Bronner et al. (2016), Germany (English)	N = 24 <u>AD Patients</u> : n=5, mild-AD, 4 females, mean age=65 (8.8), diagnosed in the past year <u>AD Caregivers</u> : n=6, referred to as “relatives” <u>AD HPs</u> : n=13 consisting of 3 physicians, 6 social education workers, 2 legal guardians, 1 nurse, 1 formal caregiver	Individual, face-to-face semi-structured interviews, lasting 30-60 minutes; Analysed using content analysis	Priority inferred : Stakeholders were asked questions relating to important medical and social decisions which occur following diagnosis of AD: As these decisions are important, one can assume the discussed outcomes are important/have priority	<u>AD Patients</u> : Patient independence and autonomy, spouses’ “duty” to care, health services and disease information <u>AD Caregivers</u> : Memory/slowing of forgetfulness, family participation in care <u>AD HPs</u> : ADL, patient independence and autonomy, driving, patient mental health, maintaining identity or personality, spouses’ “duty” to care, caregiver burden, health services and disease information, caregiver social support, delaying entry into care	<u>CASP</u> : Researchers’ own roles regarding bias not assessed <u>Other</u> : Outcome priority is inferred; Participant results cannot be split based on subgroups (i.e. spousal vs child carers); HP group contains a formal caregiver and 2 legal guardians, which may not be HPs in the classic sense (i.e. physicians, nurses, etc.)
Cheng et al. (2016), China (English)	N = 57 <u>AD Caregivers</u> : Mild-moderate AD; 10 spouses, 44 adult children, 1 daughter-in-law, 1 son-in-law, and 1 nephew; Mean age=54 (7.1)	Tape recorded diaries were kept for 8 weeks: Recorded positive aspects of caregiving; Thematic analysis applied	Priority inferred : Audio recordings were thematically analysed for a sample of caregivers, hence one can assume that categorised or discussed outcomes would be of importance / priority to this group	<u>AD Caregivers</u> : ADL, eating behaviours, stigma, spouses’ “duty” to care, caregiver social support, access to health services and disease information, patient QoL, caregiver burden	<u>CASP</u> : No issues outlined <u>Other</u> : Data relies on experiences that occurred within an 8-week period; Outcome priority is inferred; Quotes are provided for subgroups, but data analysed together meaning comparing subgroups would be biased

Dai et al. (2013), China (English)	N = 13 <u>MCI Caregivers</u> : 10 spouses, 2 adult children, 1 sibling; mean age=68.5 (12.3)	Individual, in-depth interviews conducted using broad questions relating to concerns and coping strategies surrounding caregiving for MCI; Lasted 60-180 minutes; Grounded theory applied	Priority inferred : Caregivers were asked open questions about the recent diagnosis of their family members with MCI - this led to some discussion about potential outcomes of the disease process, which were deemed important	<u>MCI Caregivers</u> : General cognitive health, patient independence and autonomy, patient mental health, stigma, health services and disease information	<u>CASP</u> : No issues outlined <u>Other</u> : Outcome priority is inferred, issue with accuracy of MCI diagnosis in this sample outlined by authors, stating that neurocognitive assessments should be used in future; Quotes are provided for subgroups, but data analysed together meaning comparing subgroups would be biased
Dean et al. (2014a), UK (English)	N = 23 <u>MCI Patients</u> : Mean age=77.8 (6.2), 10 female, diagnosed in past 6 months	Individual, in-depth semi-structured interviews conducted using topic guides developed from relevant literature; Thematic analysis applied	Priority inferred : States that thematic analysis was conducted after audiorecording and transcribing the relevant data: No further information provided, however grouping of themes suggests these outcomes hold priority or importance within the sample	<u>MCI Patients</u> : Memory/slowing of forgetfulness, language and communication, maintaining hobbies, patient social engagement, patient mental health, maintaining identity or personality, caregiver social support	<u>CASP</u> : Analysis not described in sufficient detail, researchers' own roles regarding bias not assessed <u>Other</u> : Outcome priority is inferred; Patients diagnosed using "whichever criteria the diagnosing clinician applied", which adds further heterogeneity to the sample
Dean et al. (2014b), UK (English); Same MCI patient sample as Dean et al. (2014a)	N = 43 <u>MCI Patients</u> : n=23, mean age=77.8 (range 63-86), 10 female, diagnosed in past 6 months <u>MCI Caregivers</u> : n=20, mean age=69 (range 42-84)	Individual, semi-structured interviews were conducted; Topic guides developed from relevant literature: Content analysis using grounded theory applied.	Priority inferred : Were not asked explicitly about outcomes, but the analysed responses detailed which outcomes were relevant to them regarding health services/memory clinics; hence, the discussed outcomes were deemed to hold importance/priority	<u>MCI Patients</u> : Stigma, certainty of diagnosis, access to health services and disease information <u>MCI Caregivers</u> : Health services and disease information, stigma, caregiver social support	<u>CASP</u> : Analysis not described in sufficient detail, researchers' own roles regarding bias not assessed <u>Other</u> : Outcome priority is inferred; Patients diagnosed using "whichever criteria the diagnosing clinician applied", which adds further heterogeneity to the sample
Frank et al. (2010), UK,	N = 64	Focus groups with carers and patients, lasted 90 minutes, semi-structured using open-	Priority inferred : Were not asked explicitly about outcomes, but the analysed	<u>AD Patients</u> : ADL, patient independence and autonomy	<u>CASP</u> : Recruitment strategy not discussed in sufficient detail;

US, Spain (English)	<u>AD Patients:</u> n=18, mild-moderate AD, mean age=73 (10.1), 9 female <u>AD Caregivers:</u> n=46, mean age=70 (11.2), 26 female	ended discussion; Audio recorded transcripts analysed using thematic content analysis	responses detailed which areas of dependence / autonomy were important to the patients and caregivers	<u>AD Caregivers:</u> Memory/slowing of forgetfulness, caregiver social support	researchers' own roles regarding bias not assessed <u>Other:</u> Outcome priority is inferred; Cannot compare subgroups, e.g. spouses vs child carers
Gelman (2010), USA (English)	<u>AD Caregivers:</u> Mean age=67 (range 50-75), 6 spouses, 4 adult children	Counselling sessions were conducted as opposed to research interviews, and content discussed was assessed; Contact ranged from 6 to 106 hours, with average contact being 24 hours: Content analysis applied.	Priority inferred: Data related to knowledge of AD and barriers to services and the experience of caregiving; Hence, the discussed topics were deemed to be important/priority	<u>AD Caregivers:</u> Memory/slowing of forgetfulness, patient sleep patterns, spouses' "duty" to care, caregiver burden, family participation in care, health services and disease information	<u>CASP:</u> Researchers' own roles regarding bias not assessed, no details of ethical process <u>Other:</u> Outcome priority is inferred
Gordon et al. (2015), USA (English)	<u>N = 25</u> <u>MCI Patients:</u> Mean age=78.4 (7.7), 8 females	Mixture of focus groups and individual meetings conducted, with the aim of uncovering MCI patients' symptoms and how these relate to symptoms reported by their caregiver	Priority inferred: Outcomes were not ranked for priority, however focus groups identified the range of subjects' symptoms to create a framework, indicating that these outcomes held importance / priority to the MCI patients and their caregivers	<u>MCI Patients:</u> Memory/slowing of forgetfulness, language and communication, executive functions	<u>CASP:</u> Recruitment strategy not discussed in sufficient detail; researchers' own roles regarding bias not assessed <u>Other:</u> Outcome priority is inferred; Frequency of caregiver contact with the MCI patients is not assessed, which may limit the reliability of the informed reports; Cannot compare subgroups, e.g. spouses vs child carers
Hauber et al. (2014), USA and Germany (English)	<u>N = 803</u> <u>AD Caregivers:</u> 400 from USA, 403 from Germany, mean age=47.7 (14.2)	Survey consisting of 15 best-worst scaling questions which correspond to 10 activities from the Disability Assessment for Dementia	Priority explicitly ranked: Each question presents 5 activities, and caregivers identified the activity that was most/least important to preserve: Each item was defined as preserving the ability to perform the activity for the next 36 months	<u>AD Caregivers:</u> ADL, eating behaviours	<u>NIH:</u> No issues outlined <u>Other:</u> Cannot be sure if the ranked outcomes are the preference of the patient or the caregiver: i.e. some outcomes are important as they negatively impacted the patient, as opposed to some outcomes which made care easier

Hulko (2009), Canada (English)	<i>N</i> = 4 <u>AD Patients</u> : Mean age=77: Limited data provided on the demographics of these participants other than being white and middle/upper-middle class	Series of interviews conducted: Participant observation sessions, in- home interviews lasting 40- 90 minutes, and focus groups of 2-3 hours in length: Grounded theory applied	Priority inferred : Participants spoke freely with the interviewer about the impact of AD and their experiences with the illness: Given rigorous methodology was applied to the analysis, it was assumed the discussed outcomes held importance or priority	<u>AD Patients</u> : Patient independence and autonomy, quality of patient-caregiver relationship, health services and disease information	<u>CASP</u> : No issues outlined <u>Other</u> : Small sample included, however rigorous methodology applied; Outcome priority is inferred
Jones et al. (2010), France, Germany, Italy, Spain, UK (English)	<i>N</i> = 750 <u>AD Caregivers</u> : n=250 (50 from each specified location); relationship to patient (41% adult children, 38% grandchildren, 10% spouses, 10% children-in-law). <u>AD HPs</u> : n=500 (100 from each specified location); all physicians	Surveys, consisting of a series of attitudinal statements requiring a response on a Likert-scale	Priority inferred : Stakeholders applied a value from 1 (strongly disagree) to 5 (strongly agree) to a series of attitudinal statements. Thus, greater agreement reflects greater endorsement of the statements – many of which related to AD outcomes.	<u>AD Caregivers</u> : Caregiver burden, caregiver QoL, family participation in care <u>AD HPs</u> : Caregiver QoL, health services and disease information, family participation in care	<u>NIH</u> : Sample size justification or power description not provided: However, large sample: Cannot tell if participation rate was 50%> <u>Other</u> : Outcome priority is not explicit. Caregivers' results cannot be split into subgroups.
Joosten-Weyn et al. (2008), Netherlands (English)	<i>N</i> = 8 <u>MCI Patients</u> : Diagnosed in the past 1-3 weeks, mean age=74.8 (8.1), 1 single, 5 married, 2 widowed	Individual interviews were conducted; Lasting 60-75 minutes using topic guides developed from the literature relating to diagnosis of MCI; Grounded theory applied	Priority inferred : Participants reported their experiences of MCI and how they cope with their cognitive decline, with discussion surrounding cognitive changes, their cause and consequences. Given the application of rigorous methodology and the grouping of themes, one can assume that the discussed outcomes are important	<u>MCI Patients</u> : Executive functions, physical health and mobility, patient independence and autonomy, patient mental health, maintaining identity or personality	<u>CASP</u> : Researchers' own roles regarding bias not assessed, no details of ethical process <u>Other</u> : Outcome priority is inferred: Could not analyse data based on subgroups; Small sample, however rigorous methodology applied

Kunneman et al. (2017), Netherlands (English)	<p>N = 12</p> <p><u>MCI/AD Patients:</u> n=6; age=65+ years; gender=4 male & 2 females; self-reported diagnosis: 1 MCI, 2 early AD, 3 AD.</p> <p><u>MCI/AD Caregivers:</u> n=6; age=57+ years; 4 females, 5 partners and 1 friend/ neighbour</p>	Focus groups conducted at a memory clinic; duration of 70 minutes including a 10 minute break. Audio-recordings were transcribed and content analysed.	<p>Priority inferred: Participants spoke freely about the decision-making process regarding diagnostic testing and receiving results. Transcripts were subject to rigorous content analysis, so one can assume that the resultant outcomes are of importance to the stakeholders</p>	<p><u>MCI/AD Patients:</u> Certainty of diagnosis, health services and disease information</p> <p><u>MCI/AD Caregivers:</u> Certainty of diagnosis</p>	<p><u>CASP:</u> Researchers' own roles regarding bias not assessed. <u>Other:</u> Outcome priority is inferred. Participants were recruited from those who visited the memory clinic; this excludes those who were referred by their general practitioner or those who have not sought help</p>
Kurz et al. (2008), Brazil, Canada, France, Germany, Spain, USA (English)	<p>N = 1,116</p> <p><u>AD Patients:</u> n=502; gender=246 female; location=100 USA, 100 France, 100 Germany, 100 Spain, 102 Brazil, mild-moderate AD</p> <p><u>AD Caregivers:</u> n=614; gender=465 female; location=100 USA, 100 Canada, 100 France, 100 Germany, 100 Spain, 114 Brazil</p>	Over-the-phone survey lasting 10 minutes. Statistical significance testing was applied, with 95% confidence intervals. Between-country comparisons were conducted using the student's t-test.	<p>Priority explicitly outlined: Stakeholders were asked to rate the relative importance of statements relating to AD outcomes. A higher percentage of respondents who endorsed a particular outcome infer a greater importance of that outcome</p>	<p><u>AD Patients:</u> Stability of Symptoms and general symptom control, medication side-effects, health services and disease information, patient QoL</p> <p><u>AD Caregivers:</u> Caregiver social support, medication side-effects, health services and disease information</p>	<p><u>NIH:</u> Numbers contacted for participation were not provided. <u>Other:</u> The inclusion/ exclusion criteria were not stringent. The analysis does not allow us to discern between formal and informal caregivers</p>
Lenardt et al. (2010), Brazil (Portuguese)	<p>N=14</p> <p><u>AD Caregivers:</u> Aged 22-77, 10 female, 6 spouses, 3 daughters, 1 son, 1 granddaughter, 1 sister, 1 niece, 1 female cousin: Caregivers of AD patients with mild-moderate AD</p>	Semi-structured interviews: Taxonomic, qualitative analysis applied to the data: Each domain has a specific meaning including subcategories, with results presented descriptively	<p>Priority inferred: Caregivers discussed their experiences openly regarding caring for AD patients: Analysing data into subcategories was inferred to denote priority</p>	<p><u>AD Caregivers:</u> ADL, challenging and distressing behaviours, caregiver burden, maintaining identity or personality</p>	<p><u>CASP:</u> Researchers' own roles regarding bias not assessed <u>Other:</u> Priority of outcomes is inferred: Age range of caregivers is large, but cannot compare their experiences from the data</p>
Lu & Haase (2009), USA (English)	<p>N = 10</p> <p><u>MCI Caregivers:</u> 5 males; mean age = 72 (11.22); All Caucasian; All spousal</p>	Open-ended interviews lasting 45-90 minutes. Audio-tapes were transcribed and analysed using a phenomenological approach	<p>Priority inferred: Caregivers answered open-ended questions which related to their experience of caregiving – the resultant themes</p>	<p><u>MCI Caregivers:</u> Language and communication, patient independence and autonomy, challenging and distressing behaviours, maintaining identity or</p>	<p><u>CASP:</u> Researchers' own roles regarding bias not assessed. <u>Other:</u> There is a lack of diversity of socioeconomic status and ethnicity in</p>

			inferred the importance of particular disease outcomes	personality, caregiver burden, quality of patient/caregiver relationship	this sample. Outcomes were not directly prioritised
Lu & Haase (2011), USA (English)	<i>N</i> = 18 <u>MCI Patients</u> : n=9; 7 males; mean age = 68.9 years (8.4); all Caucasian. <u>MCI Caregivers</u> : n=9; gender=7 females; mean age = 65.1 (0.97); 8 Caucasian & 1 Asian-American; All spousal	Focus groups conducted following a 'daily enhancement of meaningful activity intervention'. One round of focus groups conducted separately for patients with MCI and caregivers. A final focus group conducted with 3 spousal dyads. Data were content analysed	Priority inferred: Important outcomes were inferred from a table listed as 'Four main areas that participants thought should be included in the program', i.e. <i>what the intervention should target</i> . Thus, we can infer that these are important outcomes, but cannot infer their relative priority over one another	<u>MCI Patients</u> : ADL, patient independence and autonomy <u>MCI Caregivers</u> : Language and communication, ADL, patient mental health	<u>CASP</u> : Researchers' own roles regarding bias not assessed. <u>Other</u> : The sample lacked minority groups. Only spousal carers were included; Priority of outcomes was inferred
Malthouse & Fox. (2014), UK (English)	<i>N</i> = 10 <u>AD Patients</u> : n=5; age= 64+ years; MMSE scores between 18 & 21 <u>AD Caregivers</u> : n=5; age= 64+ years; All spousal).	Open-ended interviews, with an average duration of 40 minutes. Audio-recordings were transcribed and analysed with a six-stage thematic analysis framework.	Priority inferred: Stakeholders were asked open-ended questions regarding physical activity. The content of the resultant three themes was used to infer importance of outcomes	<u>AD Patients</u> : Patient independence and autonomy <u>AD Caregivers</u> : Physical health and mobility, patient mental health	<u>CASP</u> : Researchers' own roles regarding bias not assessed <u>Other</u> : Stakeholders were not explicitly asked to rate the importance of outcomes
MacRae (2008), Canada (English)	<i>N</i> = 8 <u>AD Patients</u> : 6 males; age = 60-85 years	In-depth, semi-structured interviews were conducted. Interview transcripts were analysed for emergent themes, using an interactionist approach.	Priority inferred: Participants responded to open-ended questions, the emerging themes inferred the importance of outcomes, but these were not explicitly prioritised.	<u>AD Patients</u> : Memory/ slowing of forgetfulness, patient independence and autonomy, delaying entry into care, maintaining identity or personality, stigma, length of patient life, patient QoL, length of patient life	<u>CASP</u> : Researchers' own role regarding bias not assessed; Findings clear but not neatly summarised; No clear ethical statement <u>Other</u> : Only one analyst; Priority of outcomes inferred
MacRae (2010), Canada (English); Includes 8 of the same participants from MacRae	<i>N</i> = 9 <u>AD Patients</u> : One more male joined this analysis, in addition to the participants from MacRae (2008): No	Again: In-depth, semi-structured interviews were conducted. Interview transcripts were analysed for	Priority inferred: Participants responded to open-ended questions, the emerging themes inferred the importance of outcomes, but	<u>AD Patients</u> : Memory/ slowing of forgetfulness, patient independence and autonomy, delaying entry into care, maintaining identity or personality, stigma,	<u>CASP</u> : Researchers' own roles regarding bias not assessed; Findings clear but not neatly summarised <u>Other</u> : Only one analyst; Priority of outcomes inferred

(2008): Outcomes from the 2 articles have been combined	further demographics presented, same as above	emergent themes, using an interactionist approach.	these were not explicitly prioritised.	length of patient life, patient QoL, length of patient life	
Naumann et al. (2011), Germany (German)	N = 35 <u>AD Caregivers</u> : 25 females; mean age= 67 years (range 43-84); 10 daughters, 3 sons, 15 wives & 7 husbands	Questionnaire approach. 25 outcome items (referred to as 'benefit aspects') were ranked. Average scores for each item were calculated.	Priority explicitly ranked: 25 itemised outcomes of AD were ranked in order of priority – the top ten were reported.	<u>AD Caregivers</u> : Language and communication, delaying entry into care, challenging and distressing behaviours, stability of symptoms and general symptom control, patient QoL	<u>CASP</u> : Recruitment strategy not discussed in great depth; ethical statement not made clear. <u>Other</u> : It is not clear where the list of 25 items came from or how it was generated.
Oremus et al. (2015), Canada (English)	N = 216 <u>AD Caregivers</u> : gender= 66% female; median age= 69 years, IQR=59-77; relationship to patient= 68% spousal, 21% parental, 9% other relative, 1% friend, <1% missing	Two-part questionnaire administered face-to-face in clinics or the participants' home. Analysis was statistical, using a regression model.	Priority explicitly outlined: Participants applied a monetary value (willingness-to-pay) to four medication scenarios offering different treatment outcomes. Higher endorsement of a scenario reflected a greater prioritisation of the corresponding treatment outcomes.	<u>AD Caregivers</u> : Medication side-effects	<u>CASP</u> : Recruitment is not described in great depth. <u>Other</u> : A limited amount of treatment outcomes are considered.
Pavarini et al. (2008), Brazil (Portuguese)	N = 14 <u>AD Caregivers</u> : 12 female, age= 39-80, had no cognitive decline based on MMSE scores	Qualitative interviews carried out in caregivers' homes guided by 2 questions: 1) How has it been to experience dementia in your family? And 2) What caregiving tasks involving activities of daily living do you need to perform for the elder?	Priority inferred: Outcomes related to experiences of caregiving for someone with AD, with statements grouped into relevant themes, indicating importance within the sample	<u>AD Caregivers</u> : Memory/ slowing of forgetfulness, ADL, caregiver burden, health services and disease information, patient social engagement, mental health, challenging and distressing behaviours, family participation in care	<u>CASP</u> : Researchers' own roles regarding bias not assessed, recruitment strategy not well described, data analysis method described but not in detail <u>Other</u> : Diagnosis states "probable AD", priority inferred, age-range of caregivers is large

Ropacki et al. (2017), USA (English) Re-analysis of participants from Gordon et al., 2015	N = 50 <u>MCI Patients:</u> n=25; 17 males; mean age =78.4 years (7.7); ethnicity; 22 Caucasians, 24 living with partner & 1 living alone. <u>MCI Caregivers:</u> n=25; 20 females; mean age=71.5 years (9.1); 22 Caucasians; 20 spouses, 2 adult children, 2 friends.	Focus groups were conducted (as in Gordon et al., 2015). Data were translated into numerical values to reflect endorsement of symptoms and concerns. Disconcordance analysis between patients and caregivers was quantitative in nature.	Priority inferred: Following focus groups, a frequency grid was used to display the prevalence of symptom / outcome concerns reported by patients and caregivers separately. The frequency of concerns was used to infer prioritisation of outcomes	<u>MCI Patients:</u> Memory/ slowing of forgetfulness, language and communication, judgement and insight, ADL, maintaining hobbies, driving, patient apathy, patient sleep patterns, patient mental health, caregiver burden, maintaining identity and personality <u>MCI Caregivers:</u> Memory/ slowing of forgetfulness, judgement and insight, ADL, maintaining hobbies, driving, patient apathy, patient sleep patterns, challenging and distressing behaviours, maintaining identity or personality, caregiver burden	<u>CASP:</u> Recruitment strategy not described in sufficient detail. <u>Other:</u> Questions were biased towards the reporting of neuropsychiatric concerns
Smith et al. (2008) Australia (English)	N = 11 <u>AD Patients:</u> n=5; age= 71-92 years; 3 males; All community-living <u>AD Caregivers:</u> n=6; age= 71-92 years; 3 males; All spousal	In-depth, semi-structured interviews conducted either at a hospital or in the participants' home. One interview was conducted over the phone. Transcripts were analysed thematically	Priority inferred: Participants were asked open-ended questions regarding their experiences with treatment. Resultant themes and concepts were considered important to the stakeholders.	<u>AD Patients:</u> Stability of symptoms and general symptom control	<u>CASP:</u> Researchers' own roles regarding bias not assessed. No clear ethical statement made. <u>Other:</u> Outcomes were not explicitly prioritised.
Smith et al. (2011), Canada (English)	N = 17 <u>AD Caregivers:</u> n=17, 25 caregivers assessed, but data relating only to AD came from 17 patients: States 13 adult children, 11 spouses and 1 in-law	In-depth narrative interviews conducted, lasting between 1 and 1.5 hours; Focus groups conducted lasting 2.5 hours; Grounded theory applied.	Priority inferred: Caregivers talked openly about their <i>expectations</i> and experiences with cholinesterase inhibitors, leading to discussion of important outcomes	<u>AD Caregivers:</u> Maintaining identity or personality, stability of symptoms and general symptom control	<u>CASP:</u> Researchers' own roles regarding bias not assessed. No clear ethical statement made. <u>Other:</u> Outcomes were not explicitly prioritised
Sorensen et al. (2008) Denmark (English)	N = 11 <u>AD Patients:</u> 5 females; mean age= 74; All living in their own home	Interviews were conducted in the patients' homes, lasting 30-90 minutes. Audio-recordings were transcribed and analysed using grounded theory	Priority inferred: Patients were asked open questions regarding coping with AD in daily life – the resultant themes and concepts were considered to be important outcomes to the patients	<u>AD Patients:</u> Maintaining hobbies, maintaining identity or personality, quality of patient-caregiver relationship	<u>CASP:</u> No issues reported <u>Other:</u> Outcomes were not explicitly prioritised.

Yektatalab et al. (2013) Iran (English)	N = 14 <u>AD HPs</u> : 11 females; age= 35-38 years, head nurses, supervisors & formal caregivers	Interviews lasted 1-2 hours. Transcripts were content analysed	Priority inferred: Caregivers were asked open-ended questions – the following thematic analysis would suggest that the discussed issues are important.	<u>AD HPs</u> : Challenging and distressing behaviours, family participation in care	<u>CASP</u> : Researchers' own roles regarding bias are not assessed. The recruitment process is not discussed in detail. <u>Other</u> : Outcomes were not prioritised.
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Note: QoL = quality of life, ADL = Activities of daily living, AD = Alzheimer's disease, HP = healthcare professional

Table 11: Study characteristics for research question 2: Meaningful delay

Author / Location	Participant Demographics	Data Collection Method	Details of Meaningful Delay in Disease Progression	Reported Meaningful Delay	Risks of Bias / Limitations
Andersen et al. (2008), Canada (English)	N = 27 <u>AD Patients:</u> n=4 females, aged 65+, early-stage AD <u>AD Caregivers:</u> n=4, 1 spouse, 2 children, 1 companion <u>AD HPs:</u> n=11, 3 physicians, 4 nurses, 4 pharmacists	Semi-structured interviews, 30-60 minutes, analytic induction applied	Meaningful delay inferred: Some evidence from pharmacists indicating that maintaining the ability to complete daily activities (e.g. functional ability, activities of daily living), patients and caregivers relating to slowing memory deterioration, and nurses relating to keeping the patient at home as long as possible	<u>AD Patients:</u> Memory/slowing of forgetfulness <u>AD Caregivers:</u> Symptom stability and general symptom control <u>AD HPs:</u> Activities of daily living, symptom stability and general symptom control, memory/slowing of forgetfulness	<u>CASP:</u> Researchers' own roles regarding bias not assessed <u>Other:</u> Sample size for each stakeholder group is small; outcomes cannot be split for caregiver subgroups (i.e. spouse/child carers); outcome priority is inferred
Rockwood et al. (2010), Canada (English)	N = 99 <u>AD HP's:</u> Clinicians involved, but cannot determine how many from the text <u>AD Patients:</u> n=99, mild-moderate AD, mean age=77 (7.7)	ADAS-Cog used to measure cognitive decline, patient/carer and clinician goal attainment (PGAS/CGAS) assessed, clinical interview based measure of change with caregiver input (CIBIC+) also used: Measured at 8 week intervals over 24 weeks.	Meaningful delay measured: Determining what would represent the minimal clinically relevant change on the ADAS-Cog, compared to PGAS, CGAS and the CIBIC+: Previous research indicates that a 4 point change on the ADAS-Cog is clinically meaningful, assess if a clinical interview based assessment of change corresponds to what is reported on the ADAS-Cog.	<u>AD HPs and AD Patients:</u> A 4 point change was related, at the group level, to improvement/decline on the other assessments: i.e., improvement on the ADAS-Cog was likely to correspond to clinically assessed improvement on the CIBIC+ overall. At the individual level, however, there was substantial variability, with agreement only ~50% across measures.	<u>NIH:</u> Loss to follow-up was approximately 24%, more than the suggested 20%. <u>Other:</u> Confidence intervals not provided for comparisons; results only relate to patients with mild-moderate AD, evidently meaningful delay will change depending on stage; Questionnaire scores were standardised for comparisons, which has implications on interpretation
Schrag & Schott (2011), UK (English)	N = 181 <u>AD HPs:</u> Clinicians involved, but cannot determine how many from the text <u>AD Patients:</u> n=181, mild AD, participants	Anchor-based method applied: Clinician assessed memory, non-memory cognitive function, the Functional Activities Questionnaire and the Clinical Dementia Rating Scale to determine clinical change: This	Meaningful delay measured: The minimal clinically relevant change on the ADAS-Cog would lie between the mean for those with no change and those with significant change judged by a clinician	<u>AD HPs and AD Patients:</u> The group with clinically relevant change at 6 months had ADAS-Cog scores between 3.1 and 3.8; the group with no change scored between 1.9 and 2.0, at 12 months the clinically relevant	<u>NIH:</u> Not clear if confounding factors such as disease stage were addressed <u>Other:</u> Results drawn from a small natural-history referring to clinically relevant decline: Not necessarily

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taken from 59 recruiting sites across the UK; mean age at baseline=75.2 (7.5);	was compared to the ADAS-Cog to determine what would be the relevant cut-off: measured at 0, 6 and 12 months	change group had with no change scored between 1.2 and 1.6: Minimal clinically relevant change was therefore determined to be 3 points on the ADAS-Cog	meaningful delay in disease progression.
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Note: QoL = quality of life, ADL = Activities of daily living, AD = Alzheimer's disease, HP = healthcare professional

Annexe VI. Thematic analysis

Table 12. Outcomes of AD across the spectrum - cognition

Theme	Stakeholder group			Supporting quotes and textual evidence:
	Patients	Caregivers	Profs	
Memory / slowing of forgetfulness	✓	✓	✓	<p><i>Patients:</i></p> <ol style="list-style-type: none"> "It'll probably help my memory you know... not wonderful, but it'll at least it should be a little better and it'll be better longer... Well I think it's supposed to slow it down a bit... I don't know how much, but I hope it slows it down quite a bit." [Early-stage AD patient regarding expectations of treatment – Andersen et al, 2008]. 'Impaired recall (for recent events, conversations, names of friends, future plans such as appointments, and location of items around the house)' emerged as an important theme during discussion with patients with MCI regarding day-to-day experiences [Dean et al, 2014a]. "Uh, my biggest beef right now is the fact that I have a hard time having a conversation with anyone and remember things like other people's names-their names, other people's names, places I've been to, things-not things I've done, but places I've been to. So it gets kind of frustrating to not be able to finish a conversation without at least having one instance where I don't remember a certain item, a name or place." [MCI patient – Gordon et al, 2015]. "It's a bloody nuisance in that I can't remember clearly things that I should remember." [Early-stage AD patient – MacRae, 2008/ 2010]. Of 25 patients with MCI, 100% were concerned about their 'memory/ recall', 88% about 'assistive devices for memory', 80% about 'memory – forgets names', 56% about 'duration of memory problems/ memory loss', and 52% about 'memory problems – affecting verbal expression'. [Ropacki et al, 2017]. <p><i>Caregivers:</i></p>

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Theme	Stakeholder group			<i>Supporting quotes and textual evidence:</i>
	Patients	Caregivers	Profs	
				<p>6. "I have several friends that are aging well but then, I mean, they're of different age groups 80, 77, 68 and they're all aging well. I mean, they don't show any signs of memory loss. They're aging very well." [Informal caregiver of a patient with MCI/ Early-AD when asked about healthy ageing – Beard et al, 2009].</p> <p>7. "One of the essential points is the deficit in short term memory. Just to accept it as it is and for Christ's sake not always spell it out..." [Caregiver of a patient with Mild-AD – Bronner et al, 2016].</p> <p>8. "It often causes trouble, if she asks me for the third time; then I don't respond to her in a friendly way..." [Caregiver of a patient with Mild-AD – Bronner et al, 2016].</p> <p>9. "I feel he could be a danger to himself simply because he forgets. It is an issue.... I'm like a safety net." [Familial caregiver of patient with mild-moderate AD – Frank et al, 2010].</p> <p>10. "I tell you that I was going crazy with worry. I was losing my mother—she was forgetting people, how to do the most basic thing—cooking rice, which she had been doing her entire life with her eyes closed, forgetting who she was. I was asking people and someone told me that building was a center for old people. And in my desperation I literally walked in off the street and asked for help. And they were able to help me." [Latino familial caregiver of a patient with AD – Gelman, 2010].</p> <p>11. Of 25 caregivers of patients with MCI, 100% were specifically concerned about 'memory/ recall', 60% about 'duration of memory problems/ memory loss', 72% about 'assistive devices for memory' and 52% about 'memory for dates' regarding the patient [Ropacki et al, 2017].</p> <p>12. "She does not remember anything, except for older memories. If you speak to her now, she will forget everything in less than two minutes." [AD Caregiver – Pavarini et al., 2008]</p> <p>13. "At times she has just had lunch and then she says that no one has given her any food" [AD Caregiver – Pavarini et al., 2008]</p> <p>14. "... it's the same topic, all day. It was tiring. She said the same thing over and over again. That made us very tired" [AD Caregiver – Pavarini et al., 2008]</p> <p><i>Healthcare professionals:</i></p> <p>15. "My understanding is that it should slow the progression of AD type dementias so that you wouldn't see as rapid deterioration in memory loss and in day to day functioning." [Nurse regarding expectations of treatment – Andersen et al, 2008]</p>
General	X	X	X	<i>Patients:</i>

Theme	Stakeholder group			<i>Supporting quotes and textual evidence:</i>
	Patients	Caregivers	Profs	
cognitive health				<p>16. "Well I hoped it would make my brain work a little better." [Early-stage AD patient regarding expectations of treatment – Andersen et al, 2008].</p> <p><i>Caregivers:</i></p> <p>17. "... of course, I like him to go out. I take a walk with him every morning and evening. I encourage him to go out to chat with the neighbours. If he always stays alone, his cognitive health will decline more quickly." [Familial caregiver of a patient with MCI – Dai et al, 2013].</p> <p><i>Healthcare professionals:</i></p> <p>18. "Umm, not to deteriorate as much, like memory wise and cognitive function." [Physician regarding expectations of treatment– Andersen et al, 2008].</p>
Language & communication	✓	✓		<p><i>Patients:</i></p> <p>19. 'Verbal difficulties (object naming and impaired verbal fluency – both spoken and written)' emerged as an important theme during discussion with patients with MCI regarding day-to-day experiences [Dean et al, 2014a].</p> <p>20. "I notice it almost primarily when we were in—in company. And have not been able to be the belle of the ball, you know. 'Cause I used to be able to tell some great jokes. But now you cannot tell jokes if you don't know the names of the people that you're talking about....Well, you don't—you don't—you tend not to talk—talk as much. You tend not—not to—you discuss family matters and things like that... Uh but you don't—you don't tell jokes. You don't uh communicate as well as with—with the crowd—with the—with a fun crowd. You know what I mean? With—if you're having a party, a birthday party or anniversary party or something." [MCI patient – Gordon et al, 2015].</p> <p>21. "I find I'm silent more than I used to be because someone else beats me to it you know. I'm thinking about what I might say and somebody over there starts to talk about it and I'm listening instead of- instead of talking about it." [MCI patient – Gordon et al, 2015].</p> <p>22. Of 25 patients with MCI, 76% were specifically concerned about 'social interaction' 56% about 'impact on social functioning'. [Ropacki et al, 2017].</p> <p><i>Caregivers:</i></p> <p>23. When asked what key areas should be targeted in an intervention for MCI, spousal caregivers of patients with MCI believed that communication skills (e.g. telling family and friends about the condition, helping the</p>

Theme	Stakeholder group			<i>Supporting quotes and textual evidence:</i>
	Patients	Caregivers	Profs	
				<p>family to understand the cognitive condition, improve communication between the patient and family/friends etc.) were a key area to target [Lu & Haase, 2011].</p> <p>24. “Sometimes it’s embarrassing because when there are people around he recedes back to his office. He is not comfortable being around large groups ... It is hard to carry on a conversation for him because people talk about politics, they talk about the war, they talk about everything and he doesn’t retain what he has heard.” [Spousal caregiver of a patient with MCI – Lu & Haase, 2009].</p> <p>25. Family caregivers of patients with AD ranked ‘Improvement to communication abilities’ as the 4th most important outcome out of a predetermined list of 25 outcomes [Naumann et al, 2011].</p>
Executive functions	✓			<p><i>Patients:</i></p> <p>26. “Uh, but uh, there again, I don’t--I don’t really have any problem when I’m thinking about one thing--I’m on the--but uh, the work that I’ve always had, has been where I had things--several balls in the air at the same time. And uh, I find I just can’t do that so much anymore. As long as I’m working on--I’m in a committee meeting, I’ve got no problem with that, or if I’m talking face-to-face with somebody with a problem, I don’t have a problem with that.” [MCI patient – Gordon et al, 2015].</p> <p>27. “Well, being a teacher, you want to give them all the directions in the order that they are, and like he says, I want to take a minute and get everything in a row. But if somebody comes in and interrupts, I can get so screwed up, what I said, and what I haven’t said yet, and what I meant to say next, and everything.” [MCI patient – Gordon et al, 2015].</p> <p>28. “The concentration problems are as bad as my forgetfulness.” [MCI patient – Joosten-Weyn et al, 2008].</p>
Judgement & insight	✓	✓		<p><i>Patients:</i></p> <p>29. “Having excellent judgement and being able to decipher changes and insight into how you were doing and rationalisation.” [MCI/ Early-AD patient when asked about healthy ageing – Beard et al, 2009].</p> <p>30. Of 25 patients with MCI, 64% were specifically concerned about ‘insight into problems’ [Ropacki et al, 2017].</p> <p><i>Caregivers:</i></p> <p>31. Of 25 caregivers of patients with MCI, 60% were specifically concerned about patients’ ‘insight into problems’. [Ropacki et al, 2017].</p>

Table 13. Outcomes of AD across the spectrum – functioning and dependency

	Stakeholder group			<i>Supporting quotes and textual evidence:</i>
	Patients	Caregivers	Profs	
Physical health & mobility	✓	✓		<p><i>Patients:</i></p> <p>32. "To be healthy and to be physically fit... to be active." [MCI/ Early-AD patient when asked about healthy ageing – Beard et al, 2009].</p> <p>33. "I am less mobile than I used to be." [MCI patient – Joosten-Weyn et al, 2008].</p> <p><i>Caregivers:</i></p> <p>34. "I just think if you keep the body active, it's gonna keep your mind active." [Spousal caregiver of a patient with AD – Malthouse & Fox, 2014].</p>
Activities of daily living	✓	✓	✓	<p><i>Patients:</i></p> <p>35. Of 25 patients with MCI, 52% were specifically concerned about 'impact on daily activities' [Ropacki et al, 2017].</p> <p>36. "Well, my husband takes care of the bills and that used to be my job but when he retired he decided he should do it and sometimes it annoys me." [Patient with mild-moderate AD – Frank et al, 2010].</p> <p>37. When asked what key areas should be targeted in an intervention for MCI, patients with MCI regarded self-management (e.g. of medications, folding laundry, and strategies for talking on the phone) as one of the four key areas to target [Lu & Haase, 2011].</p> <p><i>Caregivers:</i></p> <p>38. Caregivers of patients with MCI ranked 'MCI Patient – memory based activities of daily living' as the joint 3rd most important outcome and 'daily functioning' as the 5th most important outcome from a selection of 12 outcomes. [Barrios et al, 2016].</p> <p>39. "Today, mom saw me occupied with other things when it's almost time to cook. She took the initiative to ask whether I needed help to prepare the vegetables. I was so pleased she asked and found things to do herself. Although I had to separate the bad vegetables from the good ones after she washed them, but to her, it's a contribution made." [Daughter caregiver of a patient with MCI – Cheng et al, 2016].</p> <p>40. Caregivers of patients with AD in the US and Germany ranked the importance of 10 functional outcomes – the top two for both countries were: 1) Using the toilet without accidents, and 2) Eating meals. The following three outcomes differed between the countries but were all ranked within the top five: 3) Taking</p>

Stakeholder group			<i>Supporting quotes and textual evidence:</i>
Patients	Caregivers	Profs	
			<p>medicines (US)/ Washing and drying body completely (Germany), 4) Staying at home alone, and 5) Washing and drying body completely (US)/ Taking medicines (Germany). [Hauber et al, 2014].</p> <p>41. When asked what key areas should be targeted in an intervention for MCI, spousal caregivers of patients with MCI regarded patients' self-management (e.g. of self-care, self-administering medications, simple meal preparation, and household management) as a key area to target [Lu & Haase, 2011].</p> <p>42. Of 25 caregivers of patients with MCI, 56% were specifically concerned about patients' 'handling of money' [Ropacki et al, 2017].</p> <p>43. Of 25 caregivers of patients with MCI, 68% were specifically concerned about patients' 'cooking' [Ropacki et al, 2017].</p> <p>44. "In my opinion the shower time is quite difficult because she does not like to have a shower, so we need to ask for about an hour before she actually goes to the bathroom." [AD Carer 10 – Lenardt et al., 2010]</p> <p>45. "He does not like to have a shower, so I need to tell him to have a shower. Sometimes I help him to get dressed" [AD Carer 8 – Lenardt et al., 2010]</p> <p>46. "The hardest thing for me is showering...sometimes I cannot do it, she gets agitated, she fights, she gets violent, and refuses help. Then I stop, and I do not give her a shower, you know..." [AD Caregiver – Pavarini et al., 2008]</p> <p>47. "Showering is very difficult, we need to take her there, help her take her clothes off, we need to put the soap in her hands, give her the sponge and say: "mum, scrub here, scrub there". And help with the scrubbing. We say, "mum, use a lot of soap". Now, if you do not give her the soap, or the towel.... Her feet, you need to say: "mum, dry your feet because they are wet, I'll help". You need to help all the time" [AD Caregiver – Pavarini et al., 2008]</p> <p>48. "The hardest thing for me is the shower, I take her clothes off and she does not want to do it, I insist about three or four times, sometimes I manage to do it, sometimes I don't..." [AD Caregiver – Pavarini et al., 2008]</p> <p>49. "Sometimes she insists, and then it is more difficult to have a shower, then it scares me, you know, because if she says she will not take a shower, she will remain grubby." [AD Caregiver – Pavarini et al., 2008]</p> <p>50. "She goes in on her own. Then I taught my granddaughter... there is a gap by the bathroom door and Julia is already used to peeking...Check if grandma turned the shower on. Then Julia checks: "Great-grandma, turn it on, great-grandma, go under it"... She gives her the coordinates, you know, she checks her and gives the</p>

Stakeholder group			<i>Supporting quotes and textual evidence:</i>
Patients	Caregivers	Profs	
			<p>coordinates. But it is difficult, it is very difficult. She still does not accept it... Sometimes she is still lucid, so she... so she is not ill, you know, she is not ill." [AD Caregiver – Pavarini et al., 2008]</p> <p>51. "She would get dressed, she would get changed, but she forgot how to wear a skirt, the zipper would be in front, she would wear three of four pieces of clothing, she would wear everything she though it was hers, one on top of the other, until she could not go to bed on her own" [AD Caregiver – Pavarini et al., 2008]</p> <p>52. "...when I take her to use the toilet she forgets to lift her skirt and to take her knickers off. She just stays there. This has been happening for the past two months. It does not happen every time. She goes to the toilet to pee, but we need to remind her to do it. When she sits, we need to show everything to her. When the time comes to wash her hands, I don't know if it is because she cannot see well, I put the soap in her hands, under the water, then she realises that that's where she will wash her hands. Otherwise she does not know where to wash her hands. She will say "is it here", she gets lost." [AD Caregiver – Pavarini et al., 2008]</p> <p>53. "She has trouble going to the toilet now. She does not know how to take her knickers off. I help her, she does not want it, she is just like a child now, you know..." [AD Caregiver – Pavarini et al., 2008]</p> <p>54. "She always used to wear a skirt and a top. We are changing that now. We are using dresses because it is one piece of clothing and it is easier. When she was on her own and still wore a skirt, we would get here and see that her zipper was in front. I arrived one day, and the skirt was upside down. She used a hair pin to keep it in place." [AD Caregiver – Pavarini et al., 2008]</p> <p>55. "...gradually she forgot how to do the dishes. We could not leave the gas on that she would turn the hob on and forget about it" [AD Caregiver – Pavarini et al., 2008]</p> <p>56. "About a month ago I removed, I turned the hob off. So, I heat everything in the microwave for her, upstairs, at my son's. This is because twice she forgot the hob on while heating milk... I was busy with my granddaughter... all these issues, you know. So, the milk evaporated, it burned, the house was full of smoke.... She did not notice it. She has done it twice. There was another time when I went there, as soon as I got in I could smell the gas. The gas was on. So, I do not let her use it anymore. "Mom, are you gonna drink milk?" "Yes" ... so I heat it. I serve her food, heat it in the microwave, we sit together and eat together, you know. She can eat without help, but she does not prepare anything anymore, not even her milk, because of the accident. Do you understand? Because even when she prepares it she drinks it and then forgets that she has done it. Then I need to prepare it again." [AD Caregiver – Pavarini et al., 2008]</p>

	Stakeholder group			<i>Supporting quotes and textual evidence:</i>
	Patients	Caregivers	Profs	
				<p><i>Healthcare professionals:</i></p> <p>57. "Improve activities of daily living so far as you know... buttoning up a shirt or closing a zipper." [Physician regarding expectations of treatment – Andersen et al, 2008].</p> <p>58. "About coping with everyday life. This is the most difficult....how can I handle it, the disease and the deficits, which happen every day and everyday life constitutes a challenge." [Bronner et al, 2016].</p>
Maintain- ing hobbies	✓	✓		<p><i>Patients:</i></p> <p>59. "Daily life has changed and I have to accept that. It's no use feeling sorry about. My mother-in-law was very fond of reading. As her dementia progressed, she could no longer read. I hope it will be a long time before I reach that point, because there are still many books I want to read." [Patient with mild AD – Sorensen et al, 2008].</p> <p>60. When asked about day-to-day experiences, the concept of 'impact of MCI on hobbies' emerged as a prominent theme. [Patient with MCI - Dean et al, 2014a].</p> <p>61. Of 25 patients with MCI, 80% were specifically concerned about 'leisure activities/ hobbies' [Ropacki et al, 2017].</p> <p><i>Caregivers:</i></p> <p>62. Of 25 caregivers of patients with MCI, 72% were specifically concerned about 'leisure activities/ hobbies' of the patient [Ropacki et al, 2017].</p>
Social engage- ment	✓	✓		<p><i>Patients:</i></p> <p>63. "I think that ageing well comes if you are happy and you have people around who you like. I mean that's part of ... social support." [MCI/ Early-AD patient when asked about healthy ageing – Beard et al, 2009].</p> <p>64. 'Detrimental effects of MCI on social life/ hobbies' emerged as an important theme during discussion with patients with MCI regarding day-to-day experiences [Dean et al, 2014a].</p> <p><i>Caregivers:</i></p> <p>65. "That's how it is, she does not like many people. She likes family gatherings, but if there are too many people she says: "My head is spinning". She does not like...Ahh.... Gatherings, should preferably be in someone else's home. If they are in my house, she gets quite disturbed, because she is afraid that someone will mess with her stuff" [AD Caregiver – Pavarini et al., 2008]</p>

	Stakeholder group			<i>Supporting quotes and textual evidence:</i>
	Patients	Caregivers	Profs	
Eating behaviours		✓		<p><i>Caregivers:</i></p> <p>66. "We were having dinner. She refilled her bowl a bit after having a big bowl of rice. She seemed to have a better appetite [i.e., liked the food I cooked].... I was so, so happy." [Daughter caregiver of a patient with AD – Cheng et al, 2016].</p> <p>67. Caregivers of patients with AD in the US and Germany ranked the importance of 10 functional outcomes – 'Eating meals' was ranked as the 2nd most important functional outcome by caregivers in the US and Germany [Hauber et al, 2014].</p>
Independence & patient autonomy	✓	✓	✓	<p><i>Patients:</i></p> <p>68. "Loss of function...would change one's life... in a very negative way. The loss of independence for me is very important... that would be major. And having to depend on someone else. I'm just not able to do that. Successful, at say 80, means I'd be able to function and care for myself...stand on my own." [MCI/ Early-AD patient when asked about healthy ageing – Beard et al, 2009].</p> <p>69. "My husband talks to the physicians and is more familiar with that. I was present during the consultation, but I wasn't able to participate actively. I'm sitting nearby, half-involved. I haven't much knowledge, which my husband and the physicians have." [Mild-AD patient – Bronner et al, 2016].</p> <p>70. "And I try to do everything possible, as long as I possibly can." [Mild-AD patient – Bronner et al, 2016].</p> <p>71. "Well, I guess primarily—well, I have a husband and five children and they're always telling me what to do and that annoys me because after all, I was telling them what to do until just recently." [Patient with mild-moderate AD – Frank et al, 2010].</p> <p>72. "Interviewer - I get the sense that your independence is quite important to you. Nancy - Well, yes. I think it is to most people." [AD patient – Hulko, 2009].</p> <p>73. "My husband is controlling me, which makes me angry." [MCI patient – Joosten-Weyn et al, 2008].</p> <p>74. When asked what key areas should be targeted in an intervention for MCI, patients with MCI wanted to target communication with the spouse in order to tell the spouse not to overprotect, not to take away work too soon, and to allow the patient to do as much as independently as possible for as long as possible [Lu & Haase, 2011].</p> <p>75. "I don't think I need to join any group that is telling me what to do." [AD patient – Malthouse & Fox, 2014].</p>

Stakeholder group				<i>Supporting quotes and textual evidence:</i>
Patients	Caregivers	Profs		
				<p>76. "I don't tend to do things like I used to, you know, I kind of just went down a shop, those are the things I miss most of all . . . Just to do what I want to so, when I want to do it. I want to do things I want to do myself, on my own personally, than be, you know, be guided by someone who says you have to do this." [AD patient – Malthouse & Fox, 2014].</p> <p><i>Caregivers:</i></p> <p>77. "They can live independently without a lot of assistance. They pay their bills and they can differentiate between things that matter and things that don't matter." [Informal caregiver of a patient with MCI/ Early-AD when asked about healthy ageing – Beard et al, 2009].</p> <p>78. "... She is respected by people as before... Of course, she is respected by others. Why shouldn't people respect her? Not only outsiders but also my family members respect her like before. Son, daughter and grandchildren all respect her and respect her opinions of everything. When outsiders see her, they will greet her politely rather than talking back or dodging her." [Familial caregiver of patient with MCI – Dai et al, 2013].</p> <p>79. "I think the hardest part for me is... I don't want to ever make him feel like he is less of a person, or I don't want to degrade him or embarrass him" [Spousal caregiver of a patient with MCI – Lu & Haase, 2009].</p> <p>80. "...taking over someone's life, making decisions for them, not telling them the whole truth every time, that was a terrible thing for me." [Spousal caregiver of a patient with MCI – Lu & Haase, 2009].</p> <p>81. "We just go [along] every day as we always did. He can't be coddled, you know, to the point that I'm going to baby him, I don't think that's the way to go." [Wife of patient with early-stage AD – MacRae, 2008/ 2010].</p> <p><i>Healthcare professionals:</i></p> <p>82. "This is often the case: relatives promise their mum she never has to go in a retirement home. I think they can't imagine the consequences if their mum develops severe dementia." [Bronner et al, 2016].</p> <p>83. "The majority of the relatives would like to keep patients at home as long as possible." [Bronner et al, 2016].</p> <p>84. "The issue is: I want to maintain my autonomy. I don't want to be patronised." [Bronner et al, 2016].</p>
Driving	✓	✓	✓	<p><i>Patients:</i></p> <p>85. Of 25 patients with MCI, 52% were specifically concerned about 'changes in driving' [Ropacki et al, 2017].</p> <p><i>Caregivers:</i></p>

Stakeholder group			<i>Supporting quotes and textual evidence:</i>
Patients	Caregivers	Profs	
			86. Of 25 caregivers of patients with MCI, 64% were specifically concerned about patients' 'changes in driving' [Ropacki et al, 2017].
			<i>Healthcare professionals:</i>
			87. "A big issue is car driving. The problem is that they still drive their car and we have to fight that they give up driving....and we have to call the police" [Bronner et al, 2016].
			88. "The issue of driving is a very difficult issue, primarily for men. You don't have to stop driving immediately with getting the diagnosis, but you have to discuss it." [Bronner et al, 2016].

Table 14. Outcomes of AD across the spectrum – behavioural and neuropsychiatric

Stakeholder group			<i>Supporting quotes and textual evidence:</i>
Patients	Caregivers	Profs	
Apathy	✓	✓	<i>Caregivers:</i> 89. "[Husband] is bothering me sitting at the table all the time, and watching television. [. . .] I find myself having to do pretty much all of the household cleaning and keeping everything in order. [. . .] That sitting here, that bothers me more than anything because all I can see is him just shrivelling up and deteriorating right here in this chair. Your mind can't be active when you are sitting here in a chair." [Spousal caregiver of a patient with MCI – Blieszner & Roberto, 2010]. 90. Of 25 caregivers of patients with MCI, 60% were specifically concerned about patients' 'interest or motivation' [Ropacki et al, 2017]. <i>Healthcare professionals:</i> 91. "I expect that she will be able to be more engaged with her environment and more able to function." [Physician regarding expectations of treatment – Andersen et al, 2008].
Self-efficacy	✓		<i>Caregivers:</i> 92. Caregivers of patients with MCI ranked 'MCI Patient self-efficacy' as the 2nd most important outcome from a selection of 12 outcomes [Barrios et al, 2016].

	Stakeholder group			<i>Supporting quotes and textual evidence:</i>
	Patients	Caregivers	Profs	
Sleep patterns	✓	✓		<p><i>Patients:</i></p> <p>93. Of 25 patients with MCI, 56% were specifically concerned about ‘sleep’ [Ropacki et al, 2017].</p> <p><i>Caregivers:</i></p> <p>94. “A lot of the times his sleep is all messed up. [He will] doze off for two or three hours at a time. [Grandfather’s] sleeping pattern, he has gotten it completely backwards. He can’t sleep at night because he sleeps during the day.” [Familial caregiver of a patient with MCI – Blieszner & Roberto, 2010].</p> <p>95. “Just when I think it can’t get worse it does. I was complaining because I couldn’t sleep at night because he was walking around and yelling all night long.” [Latino familial caregiver of a patient with AD – Gelman, 2010].</p> <p>96. Of 25 caregivers of patients with MCI, 64% were specifically concerned about patients’ ‘sleep’ [Ropacki et al, 2017].</p>
Mental health	✓	✓	✓	<p><i>Patients:</i></p> <p>97. “Good health and especially mental health.” [MCI/ Early-AD patient when asked about healthy ageing – Beard et al, 2009].</p> <p>98. ‘Negative emotional reactions (irritation, frustration, anxiety, sadness, and embarrassment/ concern about others’ emerged as an important theme during discussion with patients with MCI regarding day-to-day experiences [Dean et al, 2014a].</p> <p>99. “I’ve felt sad without any obvious reason.” [MCI patient – Joosten-Weyn et al, 2008].</p> <p>100. Of 25 patients with MCI, 56% were specifically concerned about feelings of ‘irritation/irritated/irritating’ [Ropacki et al, 2017].</p> <p><i>Caregivers:</i></p> <p>101. Caregivers of patients with MCI ranked ‘MCI Patient anxiety’ as the 6th most important outcome from a selection of 12 outcomes [Barrios et al, 2016].</p> <p>102. “I would like that he go out to chat with others or to exercise. It can be helpful for emotions and mental health...” [Familial caregiver of a patient with MCI – Dai et al, 2013].</p>

Stakeholder group			Supporting quotes and textual evidence:
Patients	Caregivers	Profs	
			<p>103. When asked what key areas should be targeted in an intervention for MCI, spousal caregivers of patients with MCI believed that depression in the patient should be a key area to target [Lu & Haase, 2011].</p> <p>104. "It's quite easy for him to slip into a depression. Just sitting on the sofa and staring at the wall or television is not good. So we try to get that bit under our belts every day." [Spousal caregiver of a patient with AD – Malthouse & Fox, 2014].</p> <p>105. "She sees the towels hanging there and she thinks it is a man, she thinks that the door is open. I take it all away and she says: "someone is looking at me". At times she sees John in the living room and she says: "I am afraid of this man"" [AD Caregiver – Pavarini et al., 2008]</p> <p>106. "...she thinks that there is a man in the bathroom. She sees a man in the bathroom and she is afraid, you know. She is embarrassed to take her clothes off. I tell her: "Maria, it's just you and me". Then she takes her clothes off, and I help her. Then when it is time to take her knickers off she does not do it, because she thinks that people are looking at her. She feels embarrassed. One day she even cried, she cried and said she did not want to have a shower, so I got her dressed and not give her a shower" [AD Caregiver – Pavarini et al., 2008]</p> <p><i>Healthcare professionals:</i></p> <p>107. "They are sinking into depression.....The person concerned, many say, doesn't feel like doing anything, is retired, doesn't want any contact." [Bronner et al, 2016].</p> <p>108. "Then clients don't hear the diagnosis dementia too much; they hear rather that they have got depression." [Bronner et al, 2016].</p>
Challenging & distressing behaviours	✓	✓	<p><i>Caregivers:</i></p> <p>109. "I did the preparation for our income taxes and sent them to our accountant because I would rather have him be angry with me for an hour about doing that than have him anxious and agitated for a week while he is trying to put those figures together unsuccessfully. So I have changed my definition of what is ethical behavior and I trust God understands that,... I can't tell him everything I've done</p>

Stakeholder group				Supporting quotes and textual evidence:
Patients	Caregivers	Profs		
				<p>and everything I'm going to do every time, every day. I can't do it. I just don't have the energy to do it or to cope with the results of it." [Spousal caregiver of a patient with MCI – Lu & Haase, 2009].</p> <p>110. Family caregivers of patients with AD ranked 'Improvement of behavioural symptoms' as the 9th most important outcome from a predetermined list of 25 outcomes [Naumann et al, 2011].</p> <p>111. Of 25 caregivers of patients with MCI, 64% were specifically concerned about patients' 'frustration' [Ropacki et al, 2017].</p> <p>112. "She is worse than a child. If it is a child you can yell a bit and make threats, and they will end up doing what you want them to do. It is not like that with her. Sometimes I say something I should not have said, I feel angry and remorseful later on. I say, "let's go to bed", I put her in the bedroom, I turn around and when I see it she is already behind me." [AD Carer 2 – Lenardt et al., 2010]</p> <p>113. "...I took care of her on Saturday, and she was more agitated. She did not want to take a shower, she took half of her clothes off and she did not want to take the rest. She was horrible." [AD Caregiver – Pavarini et al., 2008]</p> <p><i>Healthcare professionals:</i></p> <p>114. "Some swear a lot and they are very bad tempered. We subconsciously keep a distance from them. Some don't even let us approach them to talk. Even when we want to give them their medications, they start yelling. They swear badly." [Formal paid caregivers of patients with AD – Yektatalab et al, 2013].</p> <p>115. "If you don't have patience here, you won't last for even 2 months because of patients' yelling and their aggression." [Formal paid caregivers of patients with AD – Yektatalab et al, 2013].</p> <p>116. "I try to control patients' aggression but my strategies are temporary. They start yelling and aggression again. Sometimes I don't know what I should do. I need more information about these patients." [Formal paid caregivers of patients with AD – Yektatalab et al, 2013].</p>
Maintain- ing identity or personality	✓	✓	✓	<p><i>Patients:</i></p> <p>117. 'Perceived change in personality' emerged as an important theme during discussion with patients with MCI regarding day-to-day experiences [Dean et al, 2014a].</p> <p>118. "I've lost my self-confidence." [MCI patient – Joosten-Weyn et al, 2008].</p>

Stakeholder group			Supporting quotes and textual evidence:
Patients	Caregivers	Profs	
			<p>119. "Well the first word that comes to my mouth is fear, becoming an infant, incontinence, not knowing who you are... I can go on and on with those kind of expressions. That's what it means to me. And, it possibly also means a long, slow deterioration." [Early-stage AD patient – MacRae, 2008/2010].</p> <p>120. "My mind is very important to me in terms of who I am and that's part of the frightening thing." [Early-stage AD patient – MacRae, 2008/ 2010].</p> <p>121. "My wife keeps correcting me and I won't stand for it. When I tell her not to reprimand me she doesn't answer. I don't think she appreciates me anymore... I am more vulnerable now and I irritate her. I am no longer the man she married... My wife talks very quickly. I use to be able to understand her but now sometimes I don't understand her." [Patient with mild AD – Sorensen et al, 2008].</p> <p><i>Caregivers:</i></p> <p>122. "My best friend [husband] has been gone. He is part of me, but he is no longer the same person... He knows me better than anybody. I just don't want to lose him ... I really miss him." [Spousal caregiver of a patient with MCI – Lu & Haase, 2009].</p> <p>123. "She's my mother still. I don't see her disappearing. I don't see her personality melting away, you know, it's still there and that's hugely important to me, you know I didn't realize, you know four years ago or five years ago if you told me that 'she had Alzheimer's or she was going to have Alzheimer's, it was going to be dreadful'..., and it's certainly heart-breaking to see what's happening to her but more because of her other physical ailments, that's what's heart-breaking, not the Alzheimer's, you know. So if Aricept is contributing to that, that's what it's done, that's what it's enabled us to have." [Daughter caregiver to mother with AD – Smith et al, 2011].</p> <p>124. "The fact that I need to compel her to remember things [...]. It is complicated to see someone who used to be a Portuguese teacher not to be able to write, read or count anymore. I think this is quite complicated, this is why I insist, and ask her to spell words, make calculations [...]. I do this because I find it difficult to face the fact that someone like her is now like this" [AD Carer 1 – Lenardt et al., 2010]</p> <p>125. Of 25 caregivers of patients with MCI, 80% were specifically concerned about patients' 'personality' [Ropacki et al, 2017].</p> <p><i>Healthcare professionals:</i></p>

Stakeholder group			<i>Supporting quotes and textual evidence:</i>
Patients	Caregivers	Profs	
			126. “Many people have got a big longing for continuing with what had been important all their life.... What represented my life, what I have always done, I would like to keep doing it.” [Bronner et al, 2016].

Table 15. *Outcomes of AD across the spectrum – social issues*

	Stakeholder group			Supporting quotes and textual evidence:
	Patients	Caregiver s	Profs	
Stigma	✓	✓		<p><i>Patients:</i></p> <p>127. "I think it's very important that people [are properly informed]. It used to be that people thought of it [dementia] as being shameful, and I think of it as a sickness, like a broken arm or leg." [Early-stage AD patient – MacRae, 2008/2010].</p> <p><i>Caregivers:</i></p> <p>128. "Before I learned about the disease, I suffered a lot and could not adjust to [the caregiving role]. Now I feel less embarrassed and much more comfortable doing it. Initially, I wasn't used to the looks people gave me when I took mom out. Now, I feel more relaxed and less stressed." [Daughter caregiver of a patient with AD – Cheng et al, 2016].</p> <p>129. "... When the doctor told us that she was diagnosed with MCI, and she has a high risk to develop AD ['laonian chidai'], my family and I couldn't accept the diagnosis of 'chidai'. Why do doctors call it 'laonian chidai'? During this interview, please call it 'jiyili zhang'ai', [which means memory decline or memory loss]... The diagnosis was made by the doctor, but we don't think that she is serious enough to match the diagnosis..." [Familial caregiver of patient with MCI – Dai et al, 2013].</p> <p>130. "Generally, I describe the disease as 'Alzheimer's disease' in English rather than 'laonian chidai' in Chinese. I tell others he will have Alzheimer's disease, and I tell him [the individual with MCI] that his problem is just memory decline ['jiyili jiantui'], otherwise, he will be unhappy..." [Familial caregiver of patient with MCI – Dai et al, 2013].</p> <p>131. "I don't. Because we haven't specifically discussed this, but I get the feeling that (my husband) wouldn't like that, because there is a certain amount of stigma attached to dementia. So no, I haven't." [Wife of patient when asked about seeking social support – Dean et al, 2014b].</p>

Table 16. Outcomes of AD across the spectrum – caregiver oriented outcomes

	Stakeholder group			<i>Supporting quotes and textual evidence:</i>
	Patients	Caregivers	Profs	
Spouses' "duty" to care	✓	✓	✓	<p><i>Patients:</i></p> <p>132. "Because I think, that husband and wife should be around for each other. And through this, my husband feels good, he is happy to do that" [AD patient discussing dynamics of care – Bronner et al., 2016].</p> <p><i>Caregivers</i></p> <p>133. "He has done some terrible things to me in this life. He cheated on me, he stole our money, he didn't take care of me when I had cancer and needed him. And now it's so hard for me to sit here and take care of him, and I know it will only get worse and he'll need more and more. But what would people say? A wife is supposed to take care of her husband." [Spousal caregiver of AD patient – Gelman, 2010].</p> <p>134. "Every morning, he gets up and goes to toilet a few times. You need to wait till he finishes before you can go.... And asking the same questions every day, so annoying. But thinking he's my dearest love, in sickness and in health, I would cheer up." [Spousal caregiver of AD patient – Cheng et al., 2016].</p> <p><i>Healthcare Professionals:</i></p> <p>135. "Duties are arranged completely differently. And the wife has to completely start learning things from the beginning and complete things e.g., forms she has never done before. These are details, but it could become very difficult in individual cases" [Professional discussing AD spousal care dynamic – Bronner et al., 2016].</p>
Caregiver burden	✓	✓	✓	<p><i>Patients:</i></p> <p>136. "...of 25 patients with MCI, 72% of patients were specifically concerned about 'impact on caregiver/informant.'" [Finding from Ropacki et al., 2017]</p> <p><i>Caregivers:</i></p> <p>137. "I used to have close friends. . . . I have not felt at liberty to do that type of thing or to keep up the correspondence because I just feel that I am needed at home. . . . I don't want to go off and leave him here and go out and have lunch with a lady or something. And most of the time we just basically stay around here." [Caregiver of patient with MCI – Blieszner & Roberto., 2010].</p> <p>138. "In general, for me, there has been no burden in caring for my mother till now. If there will be a difficulty, it must be that it will become not easy for me to care of mother as my age grows... For example, sometimes</p>

Stakeholder group			Supporting quotes and textual evidence:
Patients	Caregivers	Profs	
			when I help her to take a bath, I feel it is so hard. Usually, I'm very tired after that..." [AD caregiver – Cheng et al., 2016]
			139. "Well, you ask me how you can help. But really I wonder sometimes if I'm beyond help, if only God can help me now. I don't have papers, I don't speak English, I'm here only with my sister and her daughter. But we're all useless! [Laughs] I have arthritis, and my sister has it even worse. She can hardly walk. Her hands look like tree branches. Her daughter has two small children but has to work, so I often end up taking care of them, too, if you can believe that. And I have been taking care of my mother for nearly five years without a minute of rest." [Caregiver of patient with AD – Gelman., 2010].
			140. "Overall, approximately one third (34%) of all caregivers who responded had to reduce their working hours to care for someone with dementia. Assuming a caregiver role also required caregivers to relinquish their free time, the amount of free time lost varied from 35% in France, to 51% in Italy... Most caregivers expressed negative feelings about their role: difficult (59%), exhausting (55%), demanding (46%), stressful (45%), frustrating (40%), and depressing (36%)." [Textual finding from Jones et al., 2010].
			141. "On average, caregivers spent around 7 hours per day, 6 days per week caring for the person with AD; the average time spent caring per day and days per week was lowest in France (approximately 5 hours per day for 5 days per week; P<0.001 vs Spain; P<0.01 vs Italy; P<0.05 vs the UK), but this still represents a substantial amount of time spent caring for someone else" [Textual finding from Jones et al., 2010]
			142. "...of 25 caregivers of patients with MCI, 68% were specifically concerned about 'impact on caregiver/informant.'" [Finding from Ropacki et al., 2017]
			143. The range of distressful emotions was linked to the situations and included shock, anger, guilt, anxiety, frustration, sadness, loneliness, helplessness, worry, and uncertainty. Beth: "I felt guilty and overwhelmed and I felt frustrated, people didn't understand." [Textual finding and quote from MCI caregivers - Lu and Haase, 2009]
			144. "After he came here I had to stop working and studying, because we were afraid that he would set the house on fire. So, I am here to take care of him, feed him, tidy up the house, do the laundry." [AD Carer 12 – Lenardt et al., 2010]
			145. "I quit my job, my house, to take care of her. I do not go to the cinema, I do not go out for a walk, I do not go to the shopping mall, I do not go to the hairdresser." [AD Carer 1 – Lenardt et al., 2010]

Stakeholder group			Supporting quotes and textual evidence:
Patients	Caregivers	Profs	
			<p>146. "It is a whirlwind, as it depends on whether others are helping me. It is hard work some days [...]. I need to add my mother to the equation, so I need to give 10% of my attention to one and 90% to the other; it cannot be 50% here and 50% there" [AD Carer 3 – Lenardt et al., 2010]</p> <p>147. "It has taken away my freedom. Sometimes I do not want to make lunch, but I have to do it. I feel like I am her maid." [AD Carer 11 – Lenardt et al., 2011]</p> <p>148. Caregiver burden and caregiver depression rated as <i>lowest</i> priority outcomes [Finding from Barrios et al., 2016]</p> <p>149. "It's hard, it's hard... We need a lot of patience, we need to be very calm, because otherwise..." [AD Caregiver – Pavarini et al., 2008]</p> <p>150. "You see, it's a very difficult role, because it is irreversible." [AD Caregiver – Pavarini et al., 2008]</p> <p>151. "It is tiring, it is a bit tiring, you get more stressed out, but I am managing it." [AD Caregiver – Pavarini et al., 2008]</p> <p>152. "I am tired, with a tired mind, you know." [AD Caregiver – Pavarini et al., 2008]</p> <p>153. "...when they started treatment, then they took her for tests to check her head. At that time, I did not take care of her. Until then, my sister was doing it because I was still working. It was when I was far from everyone that it became my responsibility, and this was when we found out she had Alzheimer's disease..." [AD Caregiver – Pavarini et al., 2008]</p> <p>154. "You see....I want to make something clear. I am extremely stressed out, I am taking antidepressants, anxiolytics, and we have the same doctors, the geriatrician and the cardiologist. So, they know us both...they know about my routine. Recently I went to see the doctor... I want to stop taking medication... he doubled, he doubled my dosage, you know. Especially in the past month, I have been very, very, emotionally, mentally... Two weeks ago, I took her medication, Reminyl, I felt sick, but then I called the doctor and he said it was normal. But this is not only because I take care of her, I want to make this clear. If it was just the two of us, it would be less of a burden, you know. But I have a son, a daughter in law and a granddaughter." [AD Caregiver – Pavarini et al., 2008]</p>
			<i>Healthcare Professionals:</i>

Stakeholder group			<i>Supporting quotes and textual evidence:</i>
Patients	Caregivers	Profs	
			155. "Contrary to people with AD and spouses, nearly all professionals saw the risk that the relatives may be overburdened by making promise for future support without considering the further development of AD." [Textual finding from Bronner et al., 2016].
Caregiver Quality of Life	✓		<p><i>Caregivers:</i></p> <p>156. Out of a list of 12 MCI outcomes, caregivers of patients with MCI prioritise 'caregiver quality of life' as the third most important outcome. [Barrios et al., 2016].</p> <p>157. "Caregivers frequently reported significant changes in terms of their lifestyle, their loss of freedom, the emotional impact of caregiving, and the imposition of a physical burden." [Textual finding from Jones et al., 2010].</p>
Quality of patient- caregiver relation- ship	✓	✓	<p><i>Patients:</i></p> <p>158. "Uh, I must admit there've been times when I've felt that Sue has sort of abandoned me because she's so busy, she has so much going on and uh, she's inclined to say, 'Well, you did such and such,' uh, yes, of course I don't remember that...so I'm not, I'm not reacting properly. I should take it that it's a problem for her and the girls [daughters] and for anybody else to not understand uh, I guess I've said to myself several times, 'Oh, if only so and so could have a day feeling the way I do; that would make them understand what it's like.' Because you can't explain it as far as I'm concerned. I don't feel, uh, there are words to explain it, but I don't feel the words, the vocabulary I have will get that feeling across. Uh, but uh, I'm feeling, yeah, I think I'm feeling better. That it was a long slide down, levelled off and I sort of [clears throat] almost gave up, I mean I chat with you, sort of, what's going to happen, how long can I possibly go on like this, and then, I would say that the last two weeks, maybe three, have improved. Now that doesn't mean that every day I get up and say, 'By golly, I got this,' nothing like that. But I come down and I say to Sue, 'I think this is going to be a good day.' And there's nothing specific...it's not long before I think, oh yes, here's something that oughta be done and I'm going to tackle that first so uh, I..." [Patient with AD – Hulko., 2009].</p> <p>159. "My wife is the only security I have left. We have and we have had a happy marriage. We trust each other and we have always talked about the things that happened to us. I would be so sorry if something came between me and my wife, and next, me and my children." [Patient with AD – Sorensen et al., 2008].</p> <p>160. "My wife keeps correcting me and I won't stand for it. When I tell her not to reprimand me she doesn't answer. I don't think she appreciates me anymore... I am more vulnerable now and I irritate her. I am no</p>

Stakeholder group			Supporting quotes and textual evidence:
Patients	Caregivers	Profs	
			<p>longer the man she married... My wife talks very quickly. I use to be able to understand her but now sometimes I don't understand her." [Patient with AD – Sorensen et al., 2008].</p> <p>161. "My husband gets angry with me when I can't remember the things we have decided to do. He talks a lot about it. Sometimes I think that it is worse for him than for me, I am very fond of him." [Patient with AD – Sorensen et al., 2008].</p> <p><i>Caregivers:</i></p> <p>162. "When you have a problem in your marriage, then you have a spouse that is now sick with a memory problem, then you have a compound problem. It's one thing if you have this sweet loving relationship for 20 years and then all of a sudden you are sick. We have had a complicated marriage for 20 years and now my husband is sick. Not only is he physically sick, he [has a mental] problem. I don't know what to do with him." [MCI caregiver – Blieszner and Roberto, 2010].</p> <p>163. "My best friend [husband] has been gone. He is part of me, but he is no longer the same person... He knows me better than anybody. I just don't want to lose him ... I really miss him." [MCI Caregiver – Lu & Haase, 2009]</p> <p>164. "So it was very costly. It was costly to my marriage; it was costly personally to me because it made me feel lonely." [Caregiver of patient with MCI – Lu & Haase, 2009].</p>
Family participation in care	✓	✓	<p><i>Caregivers:</i></p> <p>165. "He loved his sister so much, and now she won't even call to see how he's doing. She's so angry that I keep insisting there's something wrong, and that he obviously 'took my side' because he hasn't called her. But of course he can't call her. This is tearing the family apart." [AD caregiver – Gelman, 2010]</p> <p>166. "They [other relatives] handle some of his financial stuff, [but] ... everybody wants to be the chief, nobody wants to be the Indian. The way I look at it, if you all want to be the chiefs, then get up here and [start] doing some of the dirty work. . . . it's so easy to call the shots over the telephone and say, "I want it done this way, I want it done that way," but they are not the ones up here doing it." [MCI caregiver – Blieszner and Roberto, 2010]</p> <p>167. Evidently not always negative: "We have wonderful friends and [son] is always there, and we couldn't ask for any better. The people at church have offered to bring meals to us. . . . And, of course, the neighbours . . . one of them that lived downstairs moved last August, and I hated to see her go because she really kept check on both of us." [MCI caregiver – Blieszner and Roberto, 2010]</p>

Stakeholder group			Supporting quotes and textual evidence:
Patients	Caregivers	Profs	
			<p>168. "Being the patient's companion is in any case.....a full-time job, with the result that I can forget about my old job.....We discussed that at that time and our sons said that they are available anytime if needed and want to support their mum" [AD caregiver – Bronner et al., 2016]</p> <p>169. "The majority of caregivers (75%) recognised the devastating effects of AD on caregivers and families." [Textual finding from Jones et al., 2010].</p> <p>170. "We are lacking moral support from all the children, they leave it all to us, myself, L. and D." [AD Caregiver – Pavarini et al., 2008]</p> <p>171. "You see, everyone has problems. They live far from my house. My older brother, he does not, He does not like the term that is used, he has OCD... obsessive compulsive disorder... I think he has driven about 10 psychologists mad. He did, he did.... So, he has problems... panic attacks, phobias. He helps me. In what way? Sometimes I talk to him. But since he has problems, you know, his options are biased, he is full of prejudice, taboos. Within his limits he tries to help. When I need to leave the house, every now and then he stays with her. But he does not have much patience anymore, because he used to live with her, before... He told me 'It is in your hands, I do not have any more patience, I cannot take it anymore'. That was before the Alzheimer's diagnosis." [AD Caregiver – Pavarini et al., 2008]</p> <p><i>Healthcare Professionals</i></p> <p>172. "If we want to keep the patients calm, we should try to include their family in care because they are dependent to their family. The family can choose their patient's room and care." [Formal carers/nurses – Yektatalab et al., 2013]</p> <p>173. 'The majority of physicians (94%) recognised the devastating effects of AD on caregivers and families' [Textual finding from Jones et al., 2010].</p>
Caregiver social support	✓	✓	<p><i>Caregivers:</i></p> <p>174. "I started to realize that I should get someone to talk to when feeling helpless sometimes. I felt better after letting everything out from within." [AD caregiver – Cheng et al., 2016].</p> <p>175. "I have mastered these issues when the other [caregivers] had not. So I tried to comfort them. They were upset because their relatives accused them of stealing or kept saying the same things over and over again.... I told them [people with this disease] don't remember what they said moments ago.... She said, "Yes!" I said, "That's why you shouldn't be bothered by these things; don't feel bad." They felt less stressed afterwards.</p>

Stakeholder group			Supporting quotes and textual evidence:
Patients	Caregivers	Profs	
			<p>I don't know if I'm becoming a teacher myself but it feels good to be able to relieve them of their tension. At least, I helped someone!" [AD caregiver – Cheng et al., 2016].</p> <p>176. "Yeah, I've got two good friends, that when I'm feeling really, wanting a good rant, I can go and have a good rant to them. And they listen very ni', you know. And that, it does make a great difference. 'Cos sometimes you just got to let it out. And once I've let it out, then I can sort of calm back down and then I can carry on then." [MCI caregiver - Dean et al., 2014b]</p> <p>177. "I don't. Because we haven't specifically discussed this, but I get the feeling that (my husband) wouldn't like that, because there is a certain amount of stigma attached to dementia. So no, I haven't." [wife of patient when asked about seeking social support – Dean et al., 2014a].</p> <p>178. "The support between us both is the most important thing. Men are a bit more independent, so sometimes we have argued about something, that he has done in good faith. I don't know, I'm aware when something isn't done well and I get angry." [AD caregiver – Frank et al., 2010].</p> <p>179. "The most commonly used services by family members or other carers across countries (excluding Brazil) are medical information about AD, significantly more common in Spain (75%) than in other countries (16% to 50%); information about research and treatments for AD, significantly more common in Germany (60%) than in the USA, Canada, or France (14% to 36%); listings of local peer support groups, significantly more common in Germany and Spain (both 70%) than in the USA, France, or Canada (31% to 53%); and social events for people living with AD, used significantly more in Spain (61%) than in other countries (14% to 33%)" [Direct quote from the textual findings of Kurz et al., 2008]</p> <p>Healthcare professionals:</p> <p>180. "Well, it is all new at the beginning and it is important for relatives to build a social network." [Bronner et al, 2016].</p>

Table 17. Outcomes of AD across the spectrum – healthcare and treatment related outcomes

	Stakeholder group			Supporting quotes and textual evidence:
	Patients	Caregivers	Profs	
Stability of symptoms and general symptom control	✓	✓	✓	<p><i>Patients:</i></p> <p>181. "When ways of improving AD medications were proposed, persons with AD from all countries thought that better control of AD symptoms was important (72% to 98% of respondents in each country) [Direct quote from the textual findings of Kurz et al., 2008].</p> <p><i>Caregivers:</i></p> <p>182. "I hope that it will hold her where she is." [When asked about expectations of ChEI's – Andersen et al., 2008].</p> <p>183. "Please keep M where she is now. Don't let her get any worse." [When asked about expectations of ChEI's – Andersen et al., 2008].</p> <p>184. "All I knew in me (sic) own mind was to stabilize her, keep things at a steady thing, so you don't get worse or, that's all I knew ... as I say stabilized, in the last 12 months I haven't noticed any difference in her." [Participant 3 – Smith et al., 2008].</p> <p>185. "He would never regain what he's lost, but it could stabilize ... and that's what we sort of virtually, what it seems to be doing. So whatever John had lost at that stage he would never regain." [Participant 4 – Smith et al., 2008].</p> <p>186. "I suppose in my naiveté I would expect that it would have a drastic impact or improvement. I think I'm more impressed now in seeing that there hasn't been ... significant change in the progress of the Alzheimer's. It's more or less stabilized." [When asked about expectations of ChEI's – Smith et al., 2011].</p> <p>187. Familial caregivers of patients with AD ranked 'Slow down the progress of the condition' as fifth most important outcome, and 'Fewer AD symptoms' as the 10th most important outcome from a list of 25 predetermined outcomes [Naumann et al, 2011].</p> <p><i>Healthcare professionals:</i></p> <p>188. "Stabilise her... if she stabilises, then she can stay in her own home as long as possible." [Nurse when asked about expectations of ChEI's – Andersen et al., 2008].</p> <p>189. "We are most likely to look at stabilisation... buy some months of at a level of function that they may not have had without being on the medication." [Physician when asked about expectations of ChEI's – Andersen et al., 2008].</p>

	Stakeholder group			<i>Supporting quotes and textual evidence:</i>
	Patients	Caregivers	Profs	
Medication side-effects	✓	✓		<p><i>Patients:</i></p> <p>190. "...better control of AD symptoms (72% to 98% of respondents in each country) and fewer bothersome side effects (63% to 96%) were the most important issues." [Direct quote from the textual findings of Kurz et al., 2008].</p> <p><i>Caregivers:</i></p> <p>191. "Family members or other carers also agreed that better control of AD symptoms (94% to 100%) and fewer bothersome side effects (84% to 100%) were important issues." [Textual finding from Kurz et al., 2008].</p> <p>192. "Caregivers attributed a higher financial 'willingness-to-pay' value to medications if they did not elicit adverse side effects. 'The odds of support were 3.4 times higher when the scenarios involved no adverse effects versus a 30% chance of adverse effects.'" [Textual finding from Oremus et al., 2015].</p>
Certainty of diagnosis	✓	✓		<p><i>Patients:</i></p> <p>193. "I don't want to put myself into a, what "I think" rather than what "I know." I'm told that I've got. Because I don't wanna type into the computer and it gives me out all these anxiety lists of things "Oh, you've got this, you look that way." I don't want any of that, you know." [Patient with MCI – Dean et al., 2014b].</p> <p>194. "I just want, if you tell me that I've got X, Y, Z, then that's what I'm gonna focus on, but I don't have an open mind to what I haven't got To "think" is one thing, but to "know" is the best thing, and that's what I want." [Patient with MCI – Dean et al., 2014b].</p> <p>195. "I'm not afraid of reality (...) so if I hear that something's wrong, I'm glad to know about it and that something can be done about it." [Patient with AD – Kunneman et al., 2017].</p> <p>196. "A relatively short conversation with a clear opinion, you have the early stages of Alzheimer's. But very little about the results of the tests, how well or badly you did (...) When we got home, we both had the feeling that we were actually missing an awful lot of information." [Patient with AD – Kunneman et al., 2017].</p> <p><i>Caregivers:</i></p> <p>197. "[that lumbar puncture was] good, because it gives you certainty that it really is Alzheimer's." [Caregiver of patient with AD – Kunneman et al., 2017].</p>

	Stakeholder group			<i>Supporting quotes and textual evidence:</i>
	Patients	Caregivers	Profs	
Delaying entry into care	✓	✓		<p><i>Patients:</i></p> <p>198. "Yeah, and we're hoping to stave that off as long as we can [going to a nursing home] but if it happened tomorrow, I wouldn't feel bad about it, you know. I mean I've had a really good life. . . . One of the things you do is you sort of review your life. . . . I mean I've just had a tremendous life. I wouldn't trade it with anyone. And when it ends, it ends, you know, I'm just grateful for all I've had, and I'm going to enjoy every minute that I've got left." [Early-stage AD patient – MacRae, 2008/ 2010].</p> <p><i>Caregivers:</i></p> <p>199. Family caregivers of patients with AD ranked 'Delay of the patient having to go into care', 'Prevention of the patient having to go into care', and 'Being able to have the patient in the home for longer as the 6th, 7th and 8th most important outcomes, respectively, from a predetermined list of 25 outcomes [Naumann et al, 2011].</p> <p><i>Healthcare Professionals</i></p> <p>200. "If she stabilises, then she can stay in her own home as long as possible" [Nurse – Andersen et al., 2008]</p> <p>201. "The majority of the relatives would like to keep patients at home as long as possible" [Healthcare professional – Bronner et al., 2016]</p>
Health services and disease information	✓	✓	✓	<p><i>Patients:</i></p> <p>202. "I'm going through a sort of ping-pong, because I've been sent here, sent to (Hospital A) for MRI scans – never seen the results of those, over, over a month ago – and I've got this other appointment in a clinic in (hospital B). So I, you know, in my head, no one's told me a single thing about this since I started, you know. And I go to the doctor, no idea. No idea where the results are going to." [MCI Patient – Dean et al., 2014b]</p> <p>203. "A relatively short conversation with a clear opinion, you have the early stages of Alzheimer's. But very little about the results of the tests, how well or badly you did (.) When we got home, we both had the feeling that we were actually missing an awful lot of information." [Patient with AD - Kunneman et al., 2017]</p> <p>204. "In the USA and Europe (but not Brazil), various services provided by AD organizations are used by persons with AD. The most commonly used services (used by at least 55% of persons in any country) are: listings of local peer support groups, significantly more commonly used in Spain (62%) than in Germany</p>

Stakeholder group			<i>Supporting quotes and textual evidence:</i>
Patients	Caregivers	Profs	
			(37%); information about new treatments for AD, used significantly more in Germany (57%) than in France (30%) or Spain (18%)” [Textual finding from Kurz et al., 2008]
			205. “The most common reasons given by persons with AD for not using AD organizations in France and the USA were they had no time (44% and 9%, respectively); the organizations were too far away or inconvenient to get to (36% and 6%); or they “did not want to think so much about AD” (20% and 18%). The single most common reason given by family members or other carers not using AD organizations in France, Canada, and the USA was that they were too far away or inconvenient to get to (48%, 2%, and 14%, respectively).” [Textual finding from Kurz et al., 2008]
			206. "This is still a mystery for me. My disease is a mystery, how this has happened...It meant, that I have to go to the psychiatric hospital, but what really takes place and what is the impact of the disease...?" [Mild-AD patient – Bronner et al, 2016].
			207. "It's awkward knowing that in front of you lies the territory we've never experienced before and that it's getting worse uh, a slippery slope which is um, uh, either you don't know whether it's steep or going to be... gradual." [AD patient – Hulko, 2009].
			<i>Caregivers:</i>
			208. "So we finally realized as she got more and more forgetful and confused that something serious and bad was happening. But we didn't know what to do. I went to our doctor, maybe 2, 3 times and he kept saying it was normal, she was getting old. And I started asking around what I could do, and who could I go to for help, but nobody could advise me because they didn't know either." [Caregiver of patient with AD – Gelman., 2010].
			209. “It made it much harder at the beginning, when I was realizing that something was wrong, but I wasn't really sure what, and all the people that I asked, the people I know, didn't know either or said it was normal, what happens to people when they get old. How could they know? The truth is we need a lot more information to get out to our community, not just in Spanish, but in ways people can understand and makes sense to them.” [Caregiver of patient with AD – Gelman., 2010].
			210. “Even within our own family and friends you wouldn't believe the things people were coming up with. For a long time his brothers and sisters kept saying there was nothing wrong with him, that everyone gets forgetful and confused as one gets older. Our next door neighbor thought that he had mercury poisoning

Stakeholder group			<i>Supporting quotes and textual evidence:</i>
Patients	Caregivers	Profs	
			<p>from eating fish, because we eat a lot of ceviche, since we're from Ecuador. His son told me he was being punished by God for abandoning him and his mother." {Caregiver of patient with AD – Gelman, 2010]</p> <p>211. "If there is something I don't understand, I will go on [the computer] and look it up. And sometimes I think I know more than [health professionals] do . . . I just want to be able, [if] something happens, where I can take care of him as far as [possible] in every situation ..." [Caregiver of AD patient – Blieszner and Roberto, 2010]</p> <p>212. "Well it was, he just sort of totally blanked me. And was talking to (my husband). And I sort of, although I don't like to, I interjected and say "Well I think you know, his specialist at the hospital said he should be checked." "Well okay then, I'll get you an appointment." It took that, which I'd rather, I think that with older people and the fact that they can do things now, that if somebody is going, the GP should be picking this up." [Caregiver of MCI patient – Dean et al., 2014b]</p> <p>213. "Well, I think they sort of gave all the information that . . . Of course, one would like them to know all the answers, but that's not possible even in the ideal world. You know, if they knew all the answers, one would love to have them. But, you know, they aren't sort of absolutely superhuman, these doctors." [Caregiver of MCI patient – Dean et al., 2014b]</p> <p>214. "Yeah, the communication has been really poor, really. Which does make you feel, in my position, I don't know how he feels, but in my position, you feel a bit well they've told me that and they're just letting me get on with it, in a way." [Caregiver of MCI patient – Dean et al., 2014b]</p> <p>215. "The questions I was being asked, you know "Did he get aggressive? Did he hit me? Did he do this, did he do that." It was all proform. Yes, it might be applicable to some people but it was totally un-applicable (to me)." [Caregiver of MCI patient – Dean et al., 2014b]</p> <p>216. 66% of caregivers believed the government does not invest nearly enough money treating AD, and that the government is a barrier to those seeking medications for AD: 57% believed that health care policy makers are not very concerned about AD [Findings from Jones et al., 2010]</p> <p>217. "He has a poor memory, but we never talk about it seriously. We did not see a doctor for this until we read the recruitment flyer on the newspaper, so we went to the memory clinics at the Zhongnan Hospital." [MCI caregiver – Dai et al., 2013]</p>

Stakeholder group			<i>Supporting quotes and textual evidence:</i>
Patients	Caregivers	Profs	
			<p>218. "... I think it is normal for her to be like this. Sometimes, she behaves just like a little child and I can understand her." [MCI caregiver – Dai et al., 2013]</p> <p>219. Experiences not always negative: "Today, mom went to the clinic for follow-up consultation.... then the center.... Everywhere she went, the staff were very nice to her. All the way, we met many people who loved my mom." [AD caregiver – Cheng et al., 2016]</p> <p>220. 66% of AD caregivers believed that the government does not invest nearly enough in treating AD, and the government is a barrier to those seeking medications for AD, with 57% believing that healthcare policy makers are not concerned about AD [Findings from Jones et al., 2010]</p> <p>221. 64% of AD caregivers believed that most people would not know the difference between the early stages of AD and normal ageing, and 66% believed most people would not recognise the early signs of AD [Findings from Jones et al., 2010]</p> <p>222. "The most commonly used services by family members or other carers across countries (excluding Brazil) are medical information about AD, significantly more common in Spain (75%) than in other countries (16% to 50%); information about research and treatments for AD, significantly more common in Germany (60%) than in the USA, Canada, or France (14% to 36%)" [Textual finding from Kurz et al., 2008]</p> <p>223. "...that's when we found that that it was Alzheimer's disease, before then they said it was normal forgetfulness. So I asked him if it was sclerosis, because I thought that sclerosis was normal with ageing instead of being a more serious disease. I though forgetfulness was normal due to ageing." [AD Caregiver – Pavarini et al., 2008]</p> <p><i>Healthcare Professionals:</i></p> <p>224. "I think, that most people struggle pretty hard to have a basic understanding, to understand a bit better what it is all about..." [Bronner et al., 2016]</p> <p>225. "The thing is mostly that another person such as a legal guardian or an authorised person should represent the dementia patient's desires....People can't imagine at the beginning that it might come to this....I think it would be easier for relatives if professionals tell them how serious it becomes if someone is in late stages of dementia." [Bronner et al, 2016].</p> <p>226. As a comparison to caregiver views (above), 50% of physicians believed that the government does not invest nearly enough in treating AD; However 29% believed the government is a barrier to those seeking</p>

Stakeholder group			<i>Supporting quotes and textual evidence:</i>
Patients	Caregivers	Profs	
			<p>medications for AD, and 36% believed that health care policy makers are not very concerned about AD [Findings from Jones et al., 2010]</p> <p>227. 77% of physicians believed that most people would not know the difference between the early stages of AD and normal ageing, and 70% believed that most people would not recognise the early signs of AD [Findings from Jones et al., 2010]</p>

Table 18. *Outcomes of AD across the spectrum – patient quality of life*

Stakeholder group			Supporting quotes and textual evidence:
Patients	Caregivers	Profs	
✓	✓	✓	<p><i>Patients:</i></p> <p>228. "Just enjoying every day, that's all... Until that stage I want to enjoy every minute." [Patient with AD – MacRae., 2008/2010].</p> <p>229. "I don't think long-term, I just say, okay I've got to enjoy as much as I can." [Patient with AD – MacRae., 2008/2010].</p> <p>230. "I mean I've just had a tremendous life. I wouldn't trade it with anyone. And when it ends, it ends, you know, I'm just grateful for all I've had, and I'm going to enjoy every minute that I've got left." [Patient with AD – MacRae., 2008/2010].</p> <p>231. "Across countries, the majority of persons with AD said that quality of life issues were important to them. Of 11 issues stated during the survey, those of greatest importance (90% of respondents rating the stated issue as 'important') were: 'Best possible quality of life' 'Keeping up a social life with family and friends;' 'Medical treatment that helps control symptoms;' 'Feeling safe and supported at home' and 'Ability to enjoy life.'" [Direct quote from textual findings of Kurz et al., 2008].</p> <p><i>Caregivers:</i></p> <p>232. Caregivers of patients with MCI ranked 'Patient QoL' as the most important outcome of MCI during a qualitative aspect of an intervention trial. [Barrios et al., 2016].</p> <p>233. "Before, I did not know why my mom acted this way. After I understood that her behaviors were due to the disease.... there were fewer misunderstandings and less miserable feelings. Instead, I would put more effort into finding ways to help her.... give her better quality of life. I won't be 'pig-headed.'" [Daughter of patient with AD – Cheng et al., 2016].</p> <p>234. Familial caregivers of AD patients ranked 'Extension of a dignified life', interpreted as quality of life, as the most important outcome from a list of 25 outcomes. [Naumann et al., 2011]</p> <p><i>Healthcare professionals:</i></p> <p>235. "It would never completely cure the family member, but it could greatly improve the quality of their life." [Physician when asked about expectations of ChEI's – Andersen et al., 2008].</p>
✓			<p><i>Patients:</i></p> <p>236. "[When you think about the future, what do you think about?] Well that writing I'm doing, living as long as possible... my latest ambition is 92." [Patient with AD – MacRae., 2008/2010].</p>

Stakeholder group			<i>Supporting quotes and textual evidence:</i>
Patients	Caregivers	Profs	
			237. "I look at it as an investment, you know, I want to live as long as I can, and stay as fit as I can." [Patient with AD - MacRae., 2008/2010].

Table 19. *Secondary analysis – outcomes of AD across the spectrum*

	Stakeholder group			Supporting quotes and textual evidence:
	Patients	Caregivers	Profs	
The difficulties and implications of caregiving when employed or as a parent to dependent children		✓		<p>Caregivers:</p> <p>238. “I have so many stresses happening right now . . . just the other day I blew a fuse and lost control. I have had that happen a couple of times. . . . I [had] my first child and my husband is not able to be here . . . my mom comes [to help with the baby]. She is physically somewhat able to lift the baby and so forth, but mentally I am afraid she is going to leave a pot on and the house is going to catch on fire” [Daughter of an AD patient – Blieszner and Roberto, 2010]</p> <p>239. “I think if it was only the Alzheimer’s that would be bad enough, but somehow I would find the strength to do it. But it is everything, and it is happening all at once. They think his colon cancer may have returned, and X Agency is accusing me of having lied about our finances and are threatening to withdraw the aide. If she’s not here, I can’t work (as a home health aide) and then I will lose the health insurance and we will literally have no money. Look at these [multiple credit card statements], so you see that I am not lying; I already have over \$60,000 in debt and no hope of ever catching up.” [AD caregiver (wife) – Gelman, 2010]</p> <p>240. “My kid phoned me and asked when I would go home to have dinner. I explained that because daddy hadn’t finished ... they should have dinner first as I would be home late.... I promised a family vacation during summer school holiday and my child said “OK” right away. I felt the understanding from my young child; it made me very pleased.” [Son of AD patient – Cheng et al., 2016]</p> <p>241. “After he came here I had to stop working and studying, because we were afraid that he would set the house on fire. So, I am here to take care of him, feed him, tidy up the house, do the laundry.” [AD Carer 12 – Lenardt et al., 2010]</p> <p>242. “...when they started treatment, then they took her for tests to check her head. At that time, I did not take care of her. Until then, my sister was doing it because I was still working. It was when I was far from everyone that it became my responsibility, and this was when we found out she had Alzheimer’s disease...” [AD Caregiver – Pavarini et al., 2008]</p> <p>243. “You see....I want to make something clear. I am extremely stressed out, I am taking antidepressants, anxiolytics, and we have the same doctors, the geriatrician and the cardiologist. So, they know us both...they know about my routine. Recently I went to see the doctor... I want to stop</p>

taking medication... he doubled, he doubled my dosage, you know. Especially in the past month, I have been very, very, emotionally, mentally... Two weeks ago, I took her medication, Reminyl, I felt sick, but then I called the doctor and he said it was normal. But this is not only because I take care of her, I want to make this clear. If it was just the two of us, it would be less of a burden, you know. But I have a son, a daughter in law and a granddaughter.” [AD Caregiver – Pavarini et al., 2008]

The difficulties and implications of caregiving as an older person	✓	<p><i>Caregivers:</i></p> <p>244. “Well, you ask me how you can help. But really I wonder sometimes if I’m beyond help, if only God can help me now. I don’t have papers, I don’t speak English, I’m here only with my sister and her daughter. But we’re all useless! [Laughs] I have arthritis, and my sister has it even worse. She can hardly walk. Her hands look like tree branches. Her daughter has two small children but has to work, so I often end up taking care of them, too, if you can believe that. And I have been taking care of my mother for nearly five years without a minute of rest.” [Elderly daughter of AD patient – Gelman, 2010]</p> <p>245. “Well, I’m concerned about forgetting myself. Seniors taking care of seniors. My own forgetting and then, you know, trying to take care of somebody else and having some kind of an ailment or — I’m concerned that if I have it, I won’t have nobody to take care of me. . . . You worry about seniors taking care of seniors.” [MCI caregiver – Blieszner and Roberto, 2010]</p> <p>246. “Well, you know, the one thing you worry about, too, in my situation anyway, if something happens to me, what on earth would happen to him? That, you know, because — you know, there’s nobody — well his family, they’re all older, you know, and he has a son, but his son is kind of incapacitated, so, there’s nobody but me, so that’s why I wonder. And, you know, you feel a little guilty, but then you [think], of making some arrangements now because at the rate I’m going I could leave any day” [MCI caregiver – Blieszner and Roberto, 2010]</p> <p>247. “Luckily, now she can basically take care of herself... I am suffering from kidney cancer, having undergone a surgery... Besides, I also suffer from diabetes, prostatitis, and anemia caused by the radiotherapy of kidney cancer... I often worry about how to take care of her if the kidney cancer recurs in me. Even though it won’t happen, I am doomed to get older and older day by day, then, who will take care of her and me? I wish that we can live together in a senior house in the future, so that maybe I can take care of her sometimes...” [Spousal caregiver of MCI patient – Dai et al., 2013]</p>
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Table 20. Meaningful Delay in Disease Progression - Cognitive

	Stakeholder group			<i>Supporting quotes and textual evidence:</i>
	Patients	Caregivers	Profs	
Memory/ Slowing of forgetfulness	✓		✓	<p><i>Patients:</i></p> <p>248. "It'll probably help my memory you know... not wonderful, but it'll at least it should be a little better and it'll be better longer... Well I think it's supposed to slow it down a bit... I don't know how much, but I hope it slows it down quite a bit." [AD patient when asked about their expectations of ChEI's – Andersen et al., 2008].</p> <p><i>Healthcare professionals:</i></p> <p>249. "My understanding is that it should slow the progression of AD type dementias so that you wouldn't see as rapid a deterioration in memory loss and in day to day functioning." [Nurse when asked about expectations of ChEI's – Andersen et al., 2008].</p> <p>250. "Umm, not to deteriorate as much, like memory wise and cognitive function." [Physician when asked about expectations of ChEI's – Andersen et al., 2008].</p>
Change on the ADAS- Cog		✓		<p><i>Healthcare professionals:</i></p> <p>251. "Improvement/decline on the ADAS-Cog (4> points) was also generally associated with improvement/decline on the PGAS, CGAS, and CIBIC+: i.e. if a participant improved on the ADAS-Cog, they likely improved on the other measures at the group level: At the individual level, however, changes/no change on the ADAS-Cog vs PGAS agreed only 50/98, 50/99 for the ADAS-Cog vs CGAS, and 44/98 for the ADAS-Cog vs CIBIC+." [Textual finding from Rockwood et al., 2010 regarding minimally clinically relevant change on the ADAS-Cog].</p> <p>252. "On the basis of this study, we suggest that the current FDA requirement for a 4-point change may be too severe and that 3 points is likely to be the most appropriate whole number for an MCRC for patients with early AD." [Textual finding from Schrag et al., 2012 regarding the minimally clinically relevant change on the ADAS-Cog].</p>

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Table 21. *Meaningful Delay in Disease Progression – Healthcare and Treatment-Related*

	Stakeholder group			<i>Supporting quotes and textual evidence:</i>
	Patients	Caregivers	Profs	
Symptom Stability and General Symptom Control		✓	✓	<p><i>Caregivers:</i></p> <p>253. "I hope that it will hold her where she is." [Caregiver of patient with AD when asked about expectations of ChEI's – Andersen et al., 2008].</p> <p>254. "Please keep M where she is now. Don't let her get any worse." [Caregiver of patient with AD when asked about expectations of ChEI's – Andersen et al., 2008].</p> <p><i>Healthcare professionals:</i></p> <p>255. "Stabilise her... if she stabilises, then she can stay in her own home as long as possible." [Nurse when asked about expectations of ChEI's – Andersen et al., 2008].</p> <p>256. "We are most likely to look at stabilisation... buy some months of at a level of function that they may not have had without being on the medication." [Physician when asked about expectations of ChEI's – Andersen et al., 2008].</p>

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Table 22. *Meaningful Delay in Disease Progression – Functioning and Dependency*

	Stakeholder group			<i>Supporting quotes and textual evidence:</i>
	Patients	Caregivers	Profs	
Activities of daily living			✓	<i>Healthcare professionals:</i> 257. "Improve activities of daily living so far as you know... buttoning up a shirt or closing a zipper." [Pharmacist when asked about expectations of ChEI's – Andersen et al., 2008].

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Annexe VII. References

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