BMJ Open

Measuring quality of life of dementia patients and their caregivers: a systematic review protocol

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2017-019082
Article Type:	Protocol
Date Submitted by the Author:	09-Aug-2017
Complete List of Authors:	Landeiro, Filipa; University of Oxford, Nuffield Department of Population Health Walsh, Katie; University of Oxford, Nuffield Department of Population Health, Health Economics Research Centre Wace, Helena; University of Oxford , Nuffield Department of Population Health, Health Economics Research Centre Roberts, Nia; University of Oxford, UK, Bodleian Health Care Libraries, Lecomte, Pascal; Novartis AG Wittenberg, Raphael; London School of Economics and Political Science, Personal Social Services Research Unit Wolstenholme, Jane; University of Oxford, Department of Public Health Handels, Ron; Maastricht University, Alzheimer Centre Limburg, Department of Psychiatry and Neuropsychology, School of Mental Health and Neurosicences; Karolinska Institute, Department of Neurobiology, Care Science and Society, Division of Neurogeriatrics Roncancio-Diaz, Emilse; GE Healthcare, Life Sciences Potashman, Michele; Biogen, Value and Access Tockhorn-Heidenreich, Antje; Eli Lilly and Company Gray, Alastair; University of Oxford, Nuffield Department of Population Health
Keywords:	Dementia < NEUROLOGY, Alzheimer's disease, quality of life, Systematic literature review, Utility

Measuring quality of life of dementia patients and their caregivers: a systematic review protocol

Filipa Landeiro, Katie Walsh, Helena Wace, Nia Roberts, Pascal Lecomte, Raphael Wittenberg, Jane Wolstenholme, Ron Handels, Emilse Roncancio-Diaz, Michele H. Potashman, Antje Tockhorn-Heidenreich, Alastair M. Gray, on behalf of the ROADMAP Group

Filipa Landeiro, Senior Researcher in Health Economics, Health Economics Research Centre, Nuffield Department of Population Health, Old Road Campus, University of Oxford, Oxford, OX3 7LF, UK

Katie Walsh, Foundation Doctor, Health Economics Research Centre, Nuffield Department of Population Health, Old Road Campus, University of Oxford, Oxford, OX3 7LF, UK

Helena Wace, Foundation Doctor, Health Economics Research Centre, Nuffield Department of Population Health, Old Road Campus, University of Oxford, Oxford, OX3 7LF, UK

Nia Roberts, Information Specialist, Bodleian Health Care Libraries, Old Road Campus, University of Oxford, Oxford, OX3 7LF, UK

Pascal Lecomte, Global Head Health Economic Modelling and Methodology, Novartis Pharma AG, 4002 Basel, Switzerland

Raphael Wittenberg, Associate Professorial Research Fellow, Personal Social Services Research Unit, London School of Economics and Political Science, Houghton Street, London WC2A 2AE, UK

Jane Wolstenholme, Senior Health Economist, Health Economics Research Centre, Nuffield Department of Population Health, Old Road Campus, University of Oxford, Oxford, OX3 7LF, UK

Ron Handels, Researcher, Alzheimer Centre Limburg, Department of Psychiatry and Neuropsychology, School for Mental Health and Neurosciences, Maastricht University, Maastricht, The Netherlands, and Department of Neurobiology, Care Science and Society, Division of Neurogeriatrics, Karolinska Institute, Stockholm, Sweden

Emilse Roncancio-Diaz, Health Economics and Outcomes Research Manager, Life Sciences, GE Healthcare, White Lion Rd, Little Chalfont, Amersham HP7 9LL, UK

Michele H. Potashman, Associate Director, Value and Access, Biogen, 225 Binney St, Cambridge MA 02139, USA

Antje Tockhorn-Heidenreich, Senior Research Scientist, Eli Lilly and Company, Erl Wood Manor, Windlesham, GU20 6PH, UK

Alastair M. Gray, Professor of Health Economics, Health Economics Research Centre, Nuffield Department of Population Health, Old Road Campus, University of Oxford, Oxford, OX3 7LF, UK

Correspondence to: Filipa Landeiro filipa.landeiro@dph.ox.ac.uk

Abstract

Introduction: Dementia is the fastest growing major cause of disability globally and has a profound impact on the quality of life (QoL) of both the patient with dementia and those that care for them. This review aims to systematically identify and synthesize the measurements of QoL for patients and their caregivers across the full spectrum of dementia, from its preceding stage of pre-dementia to end of life.

Methods and analysis: A systematic literature review was conducted in MEDLINE, Embase, CDSR, CENTRAL, DARE, NHS EED, and PsycINFO between January 1990 and the end of April 2017. Two reviewers will independently assess each study for inclusion and disagreements will be resolved by a third reviewer. Data will be extracted using a pre-defined data extraction form following best practice. Study quality will be assessed with the Effective Public Health Practice Project quality assessment tool. QoL measurements will be presented separately for patients and caregivers by instrument used and, when possible, QoL will be reported by disease type and stage of the disease. Descriptive statistics of the results will be provided. A narrative synthesis of studies will also be provided discussing differences in QoL measurements by instrument used to estimate it, type of dementia and disease severity.

Ethics and Dissemination: This systematic literature review is exempt from ethics approval because the work is carried out on published documents. The findings of the review will be disseminated in a related peer-reviewed journal and presented at conferences. They will also contribute to the work developed in the Real World Outcomes across the Alzheimer's disease spectrum for better care: multi-modal data access platform (ROADMAP).

Trial registration number: CRD42017071416

Keywords: dementia, Alzheimer's disease, patient, caregiver, carer, quality of life, systematic review, utility

Strengths of study

- This systematic literature review on quality of life of dementia patients and their caregivers is based on a detailed search strategy including studies from any country published in any language, covering the time frame from 1st January 1990 until 28th April 2017.
- The review follows robust guidelines and the quality of the papers included will be assessed using a validated tool.

Limitations of study

- The heterogeneity in the way quality of life is measured and reported may not allow for direct comparisons between studies.

Introduction

Dementia is a devastating global disease with little prospect of a cure or means of preventing its progression. In 2014, it was estimated to affect 7.1% of people aged 65 and above worldwide[1]. It is a debilitating neurodegenerative condition which causes a progressive and irreversible decline in cognitive, social and physical function. There are several types of dementia and some people may present with a combination of types. Alzheimer's disease (AD) is the most common cause of dementia, accounting for 60-80% of all cases[2]. Other causes include vascular dementia (VaD), frontotemporal dementia (FTD), dementia with Lewy bodies (DLB) and others. Irrespective of the cause, dementia results in significant decline in intellectual abilities, such as memory, and causes abnormalities in behaviour, insight and judgement, anxiety and depression, with eventual loss of physical functions and personality. This eventually becomes severe enough to interfere with a person's daily functioning and activities of daily living (ADLs).

The cognitive and functional decline associated with dementia has a profound impact on the quality of life (QoL) of both the patient and those that care for them. QoL is now recognised as an increasingly valued health outcome measure in dementia. With no cure, the focus of attention in dementia care is to promote patient well-being and to maintain optimal QoL. As QoL refers to all aspects of a person's life it can provide valuable information on the patient's self-perception of health and intervention impact. QoL measures attempt to evaluate directly the impact of dementia or interventions on people's ability to function in life. They have therefore become a key way in which to assess the effectiveness of health and social service interventions.

Dementia patients require long term care and support and the responsibility for caregiving most often falls upon informal caregivers including family members, friends and neighbours. These caregivers provide a valuable resource for dementia patients. There are over 700,000 informal caregivers of people with dementia estimated to be providing £12.4 billion of unpaid care in the UK per year[3]. The work of these caregivers is vital to support the growing number of people affected by dementia and without them the formal care system would likely collapse. The National Dementia Strategy for England[4] recognises this and supporting caregivers is now a national and international policy priority.

Given that caregivers of people with dementia are considered to be such an important resource, it is important to ensure that their own QoL is satisfactory. For many, the experience of caring for their loved ones provides personal satisfaction. However, the experience can also have a negative impact. Caregivers often have high levels of anxiety, stress and depression[5] as caring for people with dementia often places a heavy mental, physical, financial, and social burden on them. Great demands are placed on caregivers who are often elderly themselves.

As a result caregivers might find themselves neglecting their own health and QoL. This could ultimately impact on the quality of the care that they provide for people with dementia. Therefore, addressing caregivers' QoL is an important challenge.

Shearer et al.[6] conducted a systematic review of the literature on health value states for AD patients and their caregivers based on generic preference-based instruments[6]. Two recently published systematic reviews examined the factors associated with the QoL of dementia patients, either in all types of setting[7] or in long-term care facilities in particular[8]. A few reviews have identified QoL measures for dementia patients and their carers[9-11]. Caregiver burden has also been explored in a few systematic reviews, either identifying factors constituting caregiver burden on informal caregivers of dementia patients[12], exploring the role of self-efficacy in health-related QoL (HRQoL) of family carers of dementia patients[13], reviewing evidence for negative caregiver outcomes in mild cognitive impairment (MCI)[14] and synthesising risk factors, or reviewing caregiver burden and interventions for familial caregivers of Alzheimer's patients[15]. However, apart from Shearer et al.[6], none of these reviews report measurements for QoL of these patients or caregivers. Furthermore, Shearer et al.[6] did not consider dementia-specific QoL measures. This review therefore aims to address this gap in the literature by addressing the following questions:

1. What is the QoL for dementia patients across all stages of disease severity, from its preceding stage of pre-dementia to end of life?
2. What is the QoL for caregivers of dementia patients across all stages of disease severity, from its preceding stage of pre-dementia to end of life?

Methods and analysis

Protocol and registration

The preparation of this protocol followed the reporting guidelines of the Preferred Reporting

Items for Systematic Reviews and Meta-Analysis for Protocols 2015 (PRISMA-P)[16]. A completed PRISMA-P checklist is available in Supplementary file 1. The protocol was registered with the PROSPERO international prospective register of systematic reviews (registration number CRD42017071416). The systematic review manuscript will be prepared following the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) statement[17-19]. In case of amendments to this protocol, they will be reported and published with the results of the review.

Study selection criteria

Participants

The focus of this review is on adult populations reporting to have either pre-dementia or dementia, irrespective of the type and stage of the disease, and their main caregivers.

Study design

This systematic literature review will include studies reporting measurements of QoL for adult-onset pre-dementia or dementia patients and their caregivers published in peer-reviewed journals or theses. We will only include primary studies that provide quantitative results. Qualitative studies will not be included.

The following study designs will be considered for inclusion: experimental studies, quasi-experimental studies, observational studies (either prospective or retrospective) and register-based studies. In cases where multiple studies used the same patient cohort, we will use the data from the study that presented the most detailed information on QoL. Case-studies, series of case-studies, studies with sample size of 30 or less patients, trial protocols, phase I clinical trials, news articles, interviews that do not use a structured quantitative questionnaire, patient education handouts, reviews, opinion or expert articles, editorials, letters to the editor, authors and editor’s replies to comments will not be included.

Modelling studies will be excluded but studies informing the model parameters will be considered for inclusion. Similarly, existing reviews of QoL of dementia patients and their caregivers will not be included but their reference lists will be screened for additional studies. Conference abstracts will not be included. However, the abstracts will be screened to determine whether the work presented has been published in a peer-reviewed journal or thesis. If this is the case, then the published study will be considered for inclusion.

Outcomes

The outcomes of interest are:

- The QoL of patients with either pre-dementia or dementia;
- The QoL of caregivers of patients with either pre-dementia or dementia.

Where possible, the QoL of patients and their caregivers will be detailed by stage of the disease: pre-clinical dementia (biomarker positive but pre-symptomatic), early symptoms (memory and other behavioural changes), MCI, prodromal AD, mild dementia, moderate dementia, severe dementia and end of life, in order to understand how QoL evolves throughout disease progression.

Quality of life

A wide range of instruments have been developed to measure QoL. These include both generic and disease-specific instruments. Whereas generic QoL measures are universal and cover general health aspects, regardless of the presence of absence of a disease, disease-specific QoL measures target individual diseases and aim to emphasise the problems specific to patients with a specific disease, such as dementia. These generic and disease-specific instruments can be further subdivided into preference or non-preference depending on whether the index has been derived by using preference weights obtained from patients or the general public, or using simple summation of item scores.

In this review we will include any study reporting a quantitative measurement of QoL, regardless of the instrument used to estimate it.

Intervention

All types of interventions related to dementia, either symptomatic or disease modifying, will be included. We will also include studies that have not assessed any intervention.

Language

No language restrictions were applied to the search.

Setting

No geography restrictions were applied to the search.

<u>*Search strategy*</u>

Electronic databases

The selection of the electronic databases used was carried out with the assistance of an information specialist. The search terms were devised in conjunction with an information specialist based on the search strategy of a previous literature review[6]. Medical Literature Analysis and Retrieval System Online (MEDLINE), Excerpta Medica dataBASE (Embase), Cochrane Database of Systematic Reviews (CDSR), Central Register of Controlled Trials (CENTRAL), Database of Abstracts of Reviews of Effects (DARE), NHS Economic Evaluation

Database (NHS EED), and PsycINFO were searched for studies published between 1st January 1990 and 28th April 2017. Supplementary file 2 provides a description of the search terms used in each database.

Manual searches

The reference list of the studies included in this review, as well as those of previous literature reviews on QoL across the full spectrum of dementia, will be searched in order to identify additional potentially relevant studies. The studies informing the model parameters in identified modelling studies will be considered for inclusion. Conference abstracts identified through the electronic searches will be screened and manuscripts of relevant abstracts will be manually searched for.

Study selection

ENDNOTE X7, Thomson Reuters, will be used for reference management. Database results will be imported to ENDNOTE where duplicates will be removed by one reviewer (KW) based on title and first author name. Subsequently, two reviewers (FL and KW) will independently assess the titles and abstract of the studies to determine whether full text review is needed, with disagreement being resolved by a third reviewer (HW). Full text will be sought for potentially relevant studies and assessed for final inclusion by two reviewers (FL and KW) with disagreements being resolved by a third reviewer (HW). The full selection process will be presented in a flow diagram according to PRISMA guidelines[17].

Data extraction

Two of three reviewers (FL, KW and ERD) will extract the data from the final set of studies onto a data extraction form (Supplementary file 3) with disagreements being solved by the third reviewer. Two native or fluent speakers will review and extract the data for the non-English references. The following information will be extracted:

- Study details: title, author, publication details, language of the study, countries of the study;
- Study design: aim of the study, type of study, type of analysis, duration, outcomes measured, instruments used to measure them, administration mode;
- Participant information: type of participant, setting, inclusion and exclusion criteria, sample size, socio-demographic information, self or proxy-rating;
- Disease specific information: type of dementia, level of severity, instrument used to measure level of severity;
- Outcomes: outcomes measured, time points measured, subgroup analysis conducted;
- Results: QoL of patients by disease severity, QoL of caregivers by disease severity of the patients (where studies report QoL using different instruments or report the same instrument in different ways, data will be extracted for each of them);
- Conclusions: Authors conclusions.

Risk of bias (quality) assessment

The Effective Public Health Practice Project "Quality assessment tool for quantitative studies"[20] recommended by the Cochrane Public Health Group will be used to assess the quality of the studies included in this review as it covers a wide range of study designs[21]. Two of three reviewers (FL, KW and ERD) will independently assess each study and two native or fluent speakers will independently assess the quality of each of the non-English studies.

Description of studies and analysis

We expect to find a diverse range of QoL measures for both patients and caregivers. The QoL measurements will be presented separately for patients and caregivers by instrument used and, if possible, graphically. When described, distinction will be made between the different types of dementia, but with a special emphasis on Alzheimer's disease, the most common form. If possible, QoL will be reported for each stage of the disease and if the QoL was self-rated or proxy-rated informed by a caregiver or care/research professional. Descriptive statistics of the results will be provided.

A narrative synthesis of all relevant studies will be provided discussing differences in QoL measurements by instrument used to estimate it, type of dementia, disease severity, and describing study and participants' characteristics, results and author's conclusions.

In case the study does not provide all the necessary data for our analysis, we will contact the authors of the studies included in this review to attempt to retrieve it.

Ethics and dissemination

This systematic literature review is exempt from ethical approval because the work will be carried out on published documents. The studies that are included in this review will be examined to determine if ethical issues have been considered. The results of this review will be disseminated in a peer-reviewed journal and presented at conferences, and will also contribute to the Real World Outcomes across the Alzheimer's disease spectrum for better care: multi-modal data access platform (ROADMAP).

Discussion

This systematic literature review will identify and synthesize the measurements of QoL, both preference and non-preference based, for patients across the full spectrum of dementia from MCI, pre-dementia and dementia to end of life, and their caregivers. QoL is increasingly seen as an important outcome in dementia research and this level of detailed measurements of QoL will be useful and help to better inform disease progression and cost-effectiveness models of dementia.

We will present QoL measurements separately by disease type, when the information is available. The main focus of our research is on Alzheimer's disease, the most common form of dementia, but given the lack of diagnostic accuracy and the recognised overlap between different causes of dementia, all forms of dementia will be considered.

Even though HRQoL as a measurement of the health status of individuals has been used since the second half of the 20th century, it was only in the 1990s that its use increased with the introduction of instruments such as EQ-5D-3L[22] and SF-6D[23]. As such, this review will include published studies on QoL since 1990. Furthermore, no languages or geographic restrictions were applied to the searches.

In conclusion, the results of this review could inform models assessing interventions on dementia for both patients and their caregivers by providing information about patient's and caregiver's perspective on treatment benefits. Additionally, this synthesis of QoL measurements for dementia patients and their caregivers can help policy makers better understand the impact of this staggering clinical condition.

Funding

This project has received funding from the Innovative Medicines Initiative 2 Joint Undertaking under grant agreement No 116020 ("ROADMAP"). This Joint Undertaking receives support from the European Union's Horizon 2020 research and innovation programme and EFPIA.

Competing interests

FL, HW, KW, NR, RW, JW and AMG declare that they have no competing interests. PL is employed by, owns stock in, and has stock options in Novartis Pharma AG. RH has received consulting fees from Roche, Nutricia and Piramal; research grants from private/public collaborations: IMI2-ROADMAP; Alzheimer Netherlands Flutemetamol; CTMM LEARN Grant 02 N-101; and public grants from: JPND Actifcare; and JPND BIOMARKAPD. ERD is employed by GE Healthcare. MP is an employee of Biogen and owns stock in Biogen. She owns stock in a variety of companies that at times include other pharmaceutical and health care-related companies. ATH is an employee of Eli Lilly and Company Limited and owns stock in Eli Lilly and Company Limited. Novartis Pharma AG, GE Healthcare, Biogen and Eli Lilly and Company Limited are industry partners in the ROADMAP Project.

Contributors

FL designed the study and is the guarantor of the review. FL, KW and HW wrote the protocol. FL, NR, RW, JW, RH, MHP, ATH and AMG devised the search strategy. PL, RW, JW, RH, ERD, MHP, ATH, and AMG critically appraised the protocol and also contributed to its development by revising different versions. All authors read and approved the final version of the manuscript.

Acknowledgments

We would like to acknowledge the contributions of the remaining members of Work Package 5 as well as of those of the wider ROADMAP group.

References

1. Prince M, Knapp M, Guerchet M, et al. Dementia UK: update. Alzheimer’s Society 2014.
2. Association As. 2017 Alzheimer's disease facts and figures. Alzheimer's & Dementia 2017;**13**(4):325-73.
3. Lewis F, Karlsberg Schaffer S, Sussex J, et al. The trajectory of dementia in the UK—Making a difference. OHE Consulting 2014.
4. Banerjee S, Owen J. Living well with dementia: a national dementia strategy. London: Department of Health 2009.
5. Schoenmakers B, Buntinx F, Delepeleire J. Factors determining the impact of care-giving on

caregivers of elderly patients with dementia. A systematic literature review. Maturitas 2010;**66**(2):191-200.
6. Shearer J, Green C, Ritchie CW, et al. Health state values for use in the economic evaluation of treatments for Alzheimer's disease. Drugs & aging 2012;**29**(1):31-43.
7. Jing W, Willis R, Feng Z. Factors influencing quality of life of elderly people with dementia and care implications: A systematic review. Archives of Gerontology and Geriatrics 2016;**66**:23-41.
8. Beerens HC, Zwakhalen SM, Verbeek H, et al. Factors associated with quality of life of people with dementia in long-term care facilities: a systematic review. International journal of nursing studies 2013;**50**(9):1259-70.
9. Aspden T, Bradshaw SA, Playford ED, et al. Quality-of-life measures for use within care homes: a systematic review of their measurement properties. Age and Ageing 2014;**43**(5):596-603.
10. Jones C, Edwards RT, Hounsome B. Health economics research into supporting carers of people with dementia: A systematic review of outcome measures. Health and Quality of Life Outcomes 2012;**10**(1):142.
11. Algar K, Woods RT, Windle G. Measuring the quality of life and well-being of people with dementia: A review of observational measures. Dementia (London, England) 2016;**15**(4):832-57.
12. Chiao CY, Wu HS, Hsiao CY. Caregiver burden for informal caregivers of patients with dementia: A systematic review. International nursing review 2015;**62**(3):340-50.
13. Crellin NE, Orrell M, McDermott O, et al. Self-efficacy and health-related quality of life in family carers of people with dementia: a systematic review. Aging Ment Health 2014;**18**(8):954-69.
14. Seeher K, Low LF, Reppermund S, et al. Predictors and outcomes for caregivers of people with mild cognitive impairment: a systematic literature review. Alzheimer's & dementia : the journal of the Alzheimer's Association 2013;**9**(3):346-55.
15. Wennberg A. DC, Streetman-Loy B., Pham H.,. Alzheimer's Patient Familial Caregivers: A Review of Burden and Interventions. Health and Social Work 2015;**40**(4):e162-e69.
16. Shamseer L, Moher D, Clarke M, et al. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015: elaboration and explanation. Bmj 2015;**349**:g7647.
17. Moher D, Liberati A, Tetzlaff J, et al. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. PLoS med 2009;**6**(7):e1000097.
18. Liberati A, Altman DG, Tetzlaff J, et al. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: explanation and elaboration. PLoS Med 2009;**6**(7):e1000100.
19. Welch V, Petticrew M, Tugwell P, et al. PRISMA-Equity 2012 extension: reporting guidelines for systematic reviews with a focus on health equity. Revista Panamericana de Salud Pública 2013;**34**(1):60-67.
20. Thomas H. Quality assessment tool for quantitative studies. Effective Public Health Practice Project McMaster University, Toronto 2003.
21. Armijo-Olivo S, Stiles CR, Hagen NA, et al. Assessment of study quality for systematic reviews: a comparison of the Cochrane Collaboration Risk of Bias Tool and the Effective Public Health Practice Project Quality Assessment Tool: methodological research. Journal of evaluation in clinical practice 2012;**18**(1):12-18.
22. EuroQol--a new facility for the measurement of health-related quality of life. Health policy (Amsterdam, Netherlands) 1990;**16**(3):199-208.
23. Brazier J, Usherwood T, Harper R, et al. Deriving a preference-based single index from the UK SF-36 Health Survey. Journal of clinical epidemiology 1998;**51**(11):1115-28.

Supplementary file 1: PRISMA-P checklist

Section and topic	Item No.	Checklist Item	Reported on page #
A) Administrative Information			
Identification	1a	Identify the report as a protocol of a systematic review	1
Update	1b	Identify protocol as an update of a previous systematic review if applicable	n/a
Registration	2	Name of registry and registration number	2
B) Authors			
Contact		Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author	1
Contributions		Describe contributions of protocol authors and identify the guarantor of the review	1 + 12
Amendments		If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments	n/a
Support			
- Sources	5a	Indicate Sources of financial or other support for the review	12
- Sponsor	5b	Provide name for the review funder and/or sponsor	11
- Role of sponsor or funder	5c	Describe roles of funder(s), sponsor(s) and/or institution(s), if any, in developing the protocol	13
C) Introduction			
Rationale	6	Describe the rationale for the review in the context of what is already known	3 + 4
Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	4 + 5
D) Methods			
Eligibility Criteria	8	Specify the study characteristics (such as PICO, study design, setting, time frame) and report characteristics (such as years considered, language, publication status) to be used as criteria for eligibility for the review	5 + 6 + 7
Information Sources	9	Describe all intended information sources (such as electronic databases, contact with study authors, trial registers or other grey literature sources) with planned dates of coverage	7 + 8
Search Strategy	10	Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated	Supplementary file 2
E) Study Records			
Data Management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	8

Selection Process	11b	State the process that will be used for selecting studies (such as two independent reviewers) through each phase of the review (that is, screening, eligibility and inclusion in meta-analysis)	5 - 10
Data Collection Process	11c	Describe planned method of extracting data from reports (such as piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators	8 - 10 + Supplementary file 3
Data Items	12	List and define all variables for which data will be sought (such as PICO items, funding sources), any pre-planned data assumptions and simplifications	8 - 9
Outcomes and prioritization	13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	6 + 9
Section and topic	**Item No.**	**Checklist Item**	**Reported on page #**
Risk of bias in individual studies	14	Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis	9
Data Synthesis	15a	Describe criteria under which study data will be quantitatively synthesised	9 + 10
	15b	If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data and methods of combining data from studies, including any planned exploration of consistency	10
	15c	Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression)	10
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned	9 – 10
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies)	n.a.
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed	9 – 10

Supplementary file 2: Search terms

Medline

# ▲	Searches	Results
1	*dementia/ or *alzheimer disease/ or exp *dementia, vascular/ or exp *frontotemporal lobar degeneration/	98,731
2	*Cognitive Dysfunction/	4,368
3	(dementia* or alzheimer*).ti.	92,750
4	((mild* or early* or preclinical or pre-clinical) adj2 (cognitive impair* or cognitive dysfunction or cognitive decline)).ti.	5,582
5	1 or 2 or 3 or 4	118,970
6	*"Quality of Life"/	69,834
7	("quality of life" or "quality of wellbeing" or "quality of well-being").ti.	55,455
8	(qol or hqol or hrqol or hrql or hr-qol or hr-ql or euroqol or euro qol or eq5d or eq-5d or eq-vas or vas or whoqol or who qol or reqol*).ti,ab.	81,919
9	(sf6 or sf6d or sf12 or sf16 or sf20 or sf36).ti,ab.	2,656
10	((sf or shortform or short-form) adj ("6" or 6d or "12" or "16" or "20" or "36" or six or twelve or sixteen or twenty or thirtysix or thirty six)).ti,ab.	26,238
11	(icepop or icecap* or duke health profile or dhp or core outcome measure? or core om).ti,ab.	2,772
12	(aaiqol or aai-qol or cdqlp or qolas or qolad or qol-ad or qold or dqol or demqol or adrql or adrqol or oqold or oqolda or seiqol or rsoc-qol or qualid or qualidem or qwb-sa or hsq-12 or zbi or zarit or ces-d or "activity and affect indicator*" or dcm or pwbcip or pwb-cip or npi-d or ham-d or basquid or basqid or stai or stai-5 or bdi or gds or gps or hui or hui-ii or hui-iii or isd or pds or pes-ad or pesad or pes-ad-aes or pesadaes or ghq or cas or cbs or qwb or cbi or bsi or srb or phq-9).ti,ab.	82,505
13	(modified coop* or modified wonca* or "psychological well-being in cognitively impaired persons").ti,ab.	23
14	*Personal Satisfaction/ or *Patient Satisfaction/	31,894
15	((life or patient* or carer? or caregiver? or spous* or wife or wives or husband?) adj satisfaction).ti.	7,129
16	((life or patient* or carer? or caregiver? or spous* or wife or wives or husband?) adj (experience? or preference? or perspective?)).ti.	8,647
17	(wellbeing or well-being).ti.	11,493
18	((life or patient* or carer? or caregiver? or spous* or wife or wives or husband?) adj (experience? or preference? or perspective?)).ti.	8,647
19	caregiver time.ti,ab.	140
20	14 or 15 or 16 or 17 or 18 or 19	51,145
21	"surveys and questionnaires"/ or self report/	394,101
22	(questionnaire? or survey?).ti,ab.	804,666
23	self report.ti,ab.	42,432
24	((patient* or carer? or caregiver? or spous* or wife or wives or husband? or proxy) adj report?).ti,ab.	7,095
25	21 or 22 or 23 or 24	976,414

26	20 and 25	23,719
27	*Caregivers/ and *"Cost of Illness"/	1,619
28	((carer? or caregiver? or care or spous* or wife or wives or husband?) adj2 (burden* or cost?)).ti.	5,142
29	burden interview?.ti.	50
30	"value of life".ti.	87
31	*"Activities of Daily Living"/	17,986
32	("activities of daily living" or acdl or funtional status).ti.	1,772
33	*quality-adjusted life years/	1,917
34	("quality adjusted life years" or "disability adjusted life years" or qaly? or daly? or qald or qale or qtime or qualy).ti.	764
35	*Health Status/	34,353
36	*sickness impact profile/	2,623
37	(standard gamble or "time trade off" or utility index or visual analog*).ti,ab.	48,455
38	(health utilit* or disutilit* or utility value?).ti,ab.	2,889
39	health status.ti.	9,145
40	6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 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	322,206
41	5 and 40	4,530
42	limit 41 to yr="1990 -Current"	4,445
43	(case reports or clinical trial phase i or comment or editorial or letter).pt. or Clinical Trials, Phase I as Topic/ or (case report or case study or letter? or editorial).ti.	3,400,815
44	grounded theory/ or exp qualitative research/ or (qualitative research or qualitative study or qualitative interview* or grounded theory or hermeneutic*).ti,ab.	67,630
45	43 or 44	3,466,599
46	42 not 45	4,087

Embase

# ▲	Searches	Results
1	exp *dementia/ or *alzheimer's disease/	177,994
2	*cognitive impairment/	40,861
3	(dementia* or alzheimer*).ti.	119,362
4	((mild* or early* or preclinical or pre-clinical) adj2 (cognitive impair* or cognitive dysfunction or cognitive decline)).ti.	8,090
5	1 or 2 or 3 or 4	223,452
6	exp *"quality of life"/	80,143
7	("quality of life" or "quality of wellbeing" or "quality of well-being").ti.	76,232
8	(qol or hqol or hrqol or hrql or hr-qol or hr-ql or euroqol or euro qol or eq5d or eq-5d or eq-vas or vas or whoqol or who qol or reqol*).ti,ab.	129,834
9	(sf6 or sf6d or sf12 or sf16 or sf20 or sf36).ti,ab.	4,872

10	((sf or shortform or short-form) adj ("6" or 6d or "12" or "16" or "20" or "36" or six or twelve or sixteen or twenty or thirtysix or thirty six)).ti,ab.	37,206
11	(icepop or icecap* or duke health profile or dhp or core outcome measure? or core om).ti,ab.	3,316
12	(aaiqol or aai-qol or cdqlp or qolas or qolad or qol-ad or qold or dqol or demqol or adrql or adrqol or oqold or oqolda or seiqol or rsoc-qol or qualid or qualidem or qwb-sa or hsq-12 or zbi or zarit or ces-d or "activity and affect indicator*" or dcm or pwbcip or pwb-cip or npi-d or ham-d or basquid or basqid or stai or stai-5 or bdi or gds or gps or hui or hui-ii or hui-iii or isd or pds or pes-ad or pesad or pes-ad-aes or pesadaes or ghq or cas or cbs or qwb or cbi or bsi or srb or phq-9).ti,ab.	114,337
13	(modified coop* or modified wonca* or "psychological well-being in cognitively impaired persons").ti,ab.	29
14	*client satisfaction/ or *life satisfaction/	1,991
15	((life or patient* or carer? or caregiver? or spous* or wife or wives or husband?) adj satisfaction).ti.	8,839
16	((life or patient* or carer? or caregiver? or spous* or wife or wives or husband?) adj (experience? or preference? or perspective?)).ti.	11,228
17	(wellbeing or well-being).ti.	12,234
18	((life or patient* or carer? or caregiver? or spous* or wife or wives or husband?) adj (experience? or preference? or perspective?)).ti.	11,228
19	caregiver time.ti,ab.	183
20	14 or 15 or 16 or 17 or 18 or 19	33,365
21	"surveys and questionnaires"/ or self report/	582,726
22	(questionnaire? or survey?).ti,ab.	1,011,521
23	self report.ti,ab.	50,950
24	((patient* or carer? or caregiver? or spous* or wife or wives or husband? or proxy) adj report?).ti,ab.	10,383
25	21 or 22 or 23 or 24	1,187,376
26	20 and 25	14,705
27	*caregiver burden/	1,934
28	((carer? or caregiver? or care or spous* or wife or wives or husband?) adj2 (burden* or cost?)).ti.	6,435
29	burden interview?.ti.	59
30	"value of life".ti.	96
31	*"activities of daily living"/	8,385
32	("activities of daily living" or acdl or funtional status).ti.	2,164
33	*quality adjusted life year/	1,084
34	("quality adjusted life years" or "disability adjusted life years" or qaly? or daly? or qald or qale or qtime or qualy).ti.	898
35	*Health Status/	28,930
36	*sickness impact profile/	689
37	(standard gamble or "time trade off" or utility index or visual analog*).ti,ab.	64,774
38	(health utilit* or disutilit* or utility value?).ti,ab.	4,516
39	health status.ti.	9,969
40	6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 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	393,955

41	5 and 40	6,763
42	limit 41 to yr="1990 -Current"	6,613
43	(editorial or letter or note or press).pt. or "phase 1 clinical trial (topic)"/ or case report/ or (case report or case study or letter? or editorial).ti.	4,421,368
44	grounded theory/ or exp qualitative research/ or (qualitative research or qualitative study or qualitative interview* or grounded theory or hermeneutic*).ti,ab.	71,138
45	43 or 44	4,489,168
46	42 not 45	6,122

PsycINFO

# ▲	**Searches**	**Results**
1	exp *dementia/ or *alzheimer's disease/	58,737
2	*cognitive impairment/	23,977
3	(dementia* or alzheimer*).ti.	47,312
4	((mild* or early* or preclinical or pre-clinical) adj2 (cognitive impair* or cognitive dysfunction or cognitive decline)).ti.	3,675
5	1 or 2 or 3 or 4	77,854
6	exp *"quality of life"/	28,944
7	("quality of life" or "quality of wellbeing" or "quality of well-being").ti.	17,544
8	(qol or hqol or hrqol or hrql or hr-qol or hr-ql or euroqol or euro qol or eq5d or eq-5d or eq-vas or vas or whoqol or who qol or reqol*).ti,ab.	15,758
9	(sf6 or sf6d or sf12 or sf16 or sf20 or sf36).ti,ab.	243
10	((sf or shortform or short-form) adj ("6" or 6d or "12" or "16" or "20" or "36" or six or twelve or sixteen or twenty or thirtysix or thirty six)).ti,ab.	5,546
11	(icepop or icecap* or duke health profile or dhp or core outcome measure? or core om).ti,ab.	367
12	(aaiqol or aai-qol or cdqlp or qolas or qolad or qol-ad or qold or dqol or demqol or adrql or adrqol or oqold or oqolda or seiqol or rsoc-qol or qualid or qualidem or qwb-sa or hsq-12 or zbi or zarit or ces-d or "activity and affect indicator*" or dcm or pwbcip or pwb-cip or npi-d or ham-d or basquid or basqid or stai or stai-5 or bdi or gds or gps or hui or hui-ii or hui-iii or isd or pds or pes-ad or pesad or pes-ad-aes or pesadaes or ghq or cas or cbs or qwb or cbi or bsi or srb or phq-9).ti,ab.	27,360
13	(modified coop* or modified wonca* or "psychological well-being in cognitively impaired persons").ti,ab.	14
14	*client satisfaction/ or *life satisfaction/	10,500
15	((life or patient* or carer? or caregiver? or spous* or wife or wives or husband?) adj satisfaction).ti.	4,378
16	((life or patient* or carer? or caregiver? or spous* or wife or wives or husband?) adj (experience? or preference? or perspective?)).ti.	3,089
17	(wellbeing or well-being).ti.	17,565
18	((life or patient* or carer? or caregiver? or spous* or wife or wives or husband?) adj (experience? or preference? or perspective?)).ti.	3,089
19	caregiver time.ti,ab.	51

20	14 or 15 or 16 or 17 or 18 or 19	30,716
21	questionnaires/ or surveys/ or self report/	36,535
22	(questionnaire? or survey?).ti,ab.	409,092
23	self report.ti,ab.	49,405
24	((patient* or carer? or caregiver? or spous* or wife or wives or husband? or proxy) adj report?).ti,ab.	2,724
25	21 or 22 or 23 or 24	446,678
26	20 and 25	10,093
27	*caregiver burden/	4,122
28	((carer? or caregiver? or care or spous* or wife or wives or husband?) adj2 (burden* or cost?)).ti.	1,257
29	burden interview?.ti.	42
30	"value of life".ti.	33
31	*"activities of daily living"/	3,835
32	("activities of daily living" or acdl or funtional status).ti.	734
33	("quality adjusted life years" or "disability adjusted life years" or qaly? or daly? or qald or qale or qtime or qualy).ti.	142
34	(standard gamble or "time trade off" or utility index or visual analog*).ti,ab.	6,195
35	(health utilit* or disutilit* or utility value?).ti,ab.	877
36	health status.ti.	2,312
37	6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35 or 36	85,145
38	5 and 37	4,392
39	limit 38 to yr="1990 -Current"	4,344
40	case report/ or (case report or case study or letter? or editorial).ti.	62,005
41	grounded theory/ or qualitative research/ or (qualitative research or qualitative study or qualitative interview* or grounded theory or hermeneutic*).ti,ab.	61,499
42	40 or 41	122,316
43	39 not 42	4,208

Cochrane Database of Systematic Reviews, Cochrane Central Register of Controlled Trials, Database Abstract of Reviews of Effects, NHS Economic Evaluation Database

ID	Search
#1	MeSH descriptor: [Dementia] explode all trees
#2	MeSH descriptor: [Mild Cognitive Impairment] explode all trees
#3	dementia* or alzheimer*:ti (Word variations have been searched)
#4	((mild* or early* or preclinical or pre-clinical) near/2 (cognitive impair* or cognitive dysfunction or cognitive decline)):ti (Word variations have been searched)
#5	#1 or #2 or #3 or #4
#6	MeSH descriptor: [Quality of Life] explode all trees
#7	quality of life or "quality of wellbeing" or "quality of well-being":ti (Word variations have been searched)
#8	qol or hqol or hrqol or hrql or hr-qol or hr-ql or euroqol or euro qol or eq5d or eq-5d or eq-vas or vas or whoqol or who qol or reqol*:ti,ab,kw (Word variations have been searched)

#9	sf6 or sf6d or sf12 or sf16 or sf20 or sf36:ti,ab,kw (Word variations have been searched)
#10	((sf or shortform or short-form) next ("6" or 6d or "12" or "16" or "20" or "36" or six or twelve or sixteen or twenty or thirtysix or thirty six)):ti,ab,kw (Word variations have been searched)
#11	icepop or icecap* or "duke health profile" or dhp or "core outcome measure?" or "core om":ti,ab,kw (Word variations have been searched)
#12	aaiqol or aai-qol or cdqlp or qolas or qolad or qol-ad or qold or dqol or demqol or adrql or adrqol or oqold or oqolda or seiqol or rsoc-qol or qualid or qualidem or qwb-sa or hsq-12 or zbi or zarit or ces-d or "activity and affect indicator*" or dcm or pwbcip or pwb-cip or npi-d or ham-d or basquid or basqid or stai or stai-5 or bdi or gds or gps or hui or hui-ii or hui-iii or isd or pds or pes-ad or pesad or pes-ad-aes or pesadaes or ghq or cas or cbs or qwb or cbi or bsi or srb or phq-9:ti,ab,kw (Word variations have been searched)
#13	modified coop* or "modified wonca*" or "psychological well-being in cognitively impaired persons":ti,ab,kw (Word variations have been searched)
#14	MeSH descriptor: [Patient Satisfaction] this term only
#15	MeSH descriptor: [Personal Satisfaction] explode all trees
#16	((life or patient* or carer? or caregiver? or spous* or wife or wives or husband?) next satisfaction):ti,ab,kw (Word variations have been searched)
#17	((life or patient* or carer? or caregiver? or spous* or wife or wives or husband?) next (experience? or preference? or perspective?)):ti,ab,kw (Word variations have been searched)
#18	wellbeing or well-being:ti (Word variations have been searched)
#19	((life or patient* or carer? or caregiver? or spous* or wife or wives or husband?) next (experience? or preference? or perspective?)):ti,ab,kw (Word variations have been searched)
#20	caregiver time:ti,ab,kw (Word variations have been searched)
#21	((carer? or caregiver? or care or spous* or wife or wives or husband?) near/2 (burden* or cost?)):ti,ab,kw (Word variations have been searched)
#22	burden interview?:ti,ab,kw (Word variations have been searched)
#23	value of life:ti,ab,kw (Word variations have been searched)
#24	MeSH descriptor: [Activities of Daily Living] explode all trees
#25	activities of daily living or acdl or "funtional status":ti,ab,kw (Word variations have been searched)
#26	MeSH descriptor: [Quality-Adjusted Life Years] explode all trees
#27	quality adjusted life years or "disability adjusted life years" or qaly? or daly? or qald or qale or qtime or qualy:ti,ab,kw (Word variations have been searched)
#28	MeSH descriptor: [Health Status] this term only
#29	MeSH descriptor: [Sickness Impact Profile] explode all trees
#30	standard gamble or "time trade off" or "utility index" or "visual analog*":ti,ab,kw (Word variations have been searched)
#31	health utilit* or disutilit* or "utility value?":ti,ab,kw (Word variations have been searched)
#32	HEALTH STATUS:ti (Word variations have been searched)
#33	#6 or #7 or #8 or #9 or #10 or #11 or #12 or #13 or #14 or #15 or #16 or #17 or #18 or #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
#34	#5 and #33

Supplementary file 3: Data extraction form

QoL Data Extraction Form

Study ID *(surname of first author and year first full report of study was published e.g. Smith 2001)*	
Publication Title	
Notes:	

General Information

Date when form was completed *(dd/mm/yyy)*	
Name of person extracting data	
Language of study	
Corresponding author contact details	
Publication type (e.g. full report, abstract, letter)	
Notes:	

Study Design

	Descriptions as stated in the study	
Aim of the study		
Type of study	Interventional study:	
	Randomised controlled trial	☐
	Non-randomised controlled trial	☐
	Cross-over randomised controlled trial	☐
	Before-and-after study	☐
	Observational study:	
	Case-control study	☐
	Cohort study	☐
	Cross-sectional study	☐
	Other (specify):	
	Register based study	☐
	Other design (specify):	
Type of analysis	Prospective	☐
	Retrospective	☐
	Unclear	☐
QoL instrument(s)		

QoL instrument language	
QoL instrument mode of administration (e.g. paper copy; electronic; telephone; face-to-face interview)	
Outcomes measured other than QoL?	
Start date	
End date	
Follow up (in months)	
Ethical approval needed/ obtained for study	☐ Yes ☐ No ☐ Unclear

Participants

	Description as stated in paper/report
Country (ies)	
Population Description	
Type of Participant	Patients ☐ Caregivers ☐ Other: ……………………………………… ☐
Setting	Community ☐ Institutional ☐ Primary Care ☐ Secondary Care ☐ Tertiary Care ☐ Mixed ☐ Unclear ☐ Other: …………………………… ☐
Enrolment Eligibility A. Inclusion Criteria B. Exclusion Criteria	 A. B.
Recruitment Process	
Sample Size	
Mean age of patients	
Patients gender (% of females in the sample)	
Mean age of caregiver	
Caregiver gender (% of females in the sample)	
Caregiver relationship to patient	Spouse ______% Daughter/son-in-law ______% Daughter ______% Grandchild ______%

	Son ______% Friend ______% Brother ______% Other: ________________ and ______% Sister ______%
Any other relevant sociodemographic information	
Notes:	

Dementia Diagnosis

	Description as stated in paper/report
Type of Dementia	Alzheimer's Disease ☐ Lewy Body Dementia ☐ Vascular Dementia ☐ Mixed ☐ Other: .... ☐
Disease Severity	Pre-clinical dementia ☐ Early symptoms ☐ MCI ☐ Prodromal AD ☐ Mild dementia ☐ Moderate dementia ☐ Severe dementia ☐ End of Life ☐
Assessment of Disease Severity	Tool Used: .... Details:
Notes	

Interventions

	Description as stated in paper/report	
Type of Intervention		
Timing of Intervention		
Duration of Intervention Period		
No. of people in each group	Comparison Group	Intervention Group
Implementation		

Outcomes

	Description as stated in paper/report
Outcome Measure	

Time Points Measured	Single Time Point Only ☐ Baseline ☐ Follow Up – Details: ………………………… ☐
Group Measured	Patient ☐ Caregiver ☐
Source *(who the information on outcome measured is obtained from)*	Patient ☐ Caregiver ☐ Clinician ☐ General public ☐ Other: ……………………………………… ☐
Tool Used	
Details	Score Range: …………………
Outcome tool validated	Yes ☐ No ☐ Unclear ☐
Notes	

Results

	Description as stated in paper/report								
Results	Pre-clinical	Early symptoms	MCI	Prodromal AD	Mild dementia	Moderate dementia	Severe dementia	End of Life	Total
Patients' QoL: A. Baseline B. Follow-up									
Caregivers' QoL: A. Baseline B. Follow-up									

Comparison Group:	Baseline	Follow Up	Effect Size	95% CIs
Intervention Group	Baseline	Follow Up	Effect Size	95% CIs

Statistical Analysis	
Conclusion	
Any other results reported?	

Conclusions

	Description as stated in paper/report
Author's conclusions	
Reviewer's conclusions	
Correspondence required for further study information *(from whom, what and when)*	
Notes	

BMJ Open

Measuring quality of life of people with pre-dementia and dementia and their caregivers: a systematic review protocol

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2017-019082.R1
Article Type:	Protocol
Date Submitted by the Author:	03-Jan-2018
Complete List of Authors:	Landeiro, Filipa; University of Oxford, Nuffield Department of Population Health Walsh, Katie; University of Oxford, Nuffield Department of Population Health, Health Economics Research Centre Ghinai, Isaac; University of Oxford Health Economics Research Centre Mughal, Seher; University of Oxford Health Economics Research Centre Nye, Elsbeth; University of Oxford Health Economics Research Centre Wace, Helena; University of Oxford , Nuffield Department of Population Health, Health Economics Research Centre Roberts, Nia; University of Oxford, UK, Bodleian Health Care Libraries, Lecomte, Pascal; Novartis AG Wittenberg, Raphael; London School of Economics and Political Science, Personal Social Services Research Unit Wolstenholme, Jane; University of Oxford, Department of Public Health Handels, Ron; Maastricht University, Alzheimer Centre Limburg, Department of Psychiatry and Neuropsychology, School of Mental Health and Neurosicences; Karolinska Institute, Department of Neurobiology, Care Science and Society, Division of Neurogeriatrics Roncancio-Diaz, Emilse; GE Healthcare, Life Sciences Potashman, Michele; Biogen, Value and Access Tockhorn-Heidenreich, Antje; Eli Lilly and Company Gray, Alastair; University of Oxford, Nuffield Department of Population Health
Primary Subject Heading:	Geriatric medicine
Secondary Subject Heading:	Health economics, Mental health, Neurology, Public health
Keywords:	Dementia < NEUROLOGY, Alzheimer's disease, quality of life, Systematic literature review, Utility

Measuring quality of life of people with pre-dementia and dementia and their caregivers: a systematic review protocol

Filipa Landeiro, Katie Walsh, Isaac Ghinai, Seher Mughal, Elsbeth Nye, Helena Wace, Nia Roberts, Pascal Lecomte, Raphael Wittenberg, Jane Wolstenholme, Ron Handels, Emilse Roncancio-Diaz, Michele H. Potashman, Antje Tockhorn-Heidenreich, Alastair M. Gray, on behalf of the ROADMAP Group

Filipa Landeiro, Senior Researcher in Health Economics, Health Economics Research Centre, Nuffield Department of Population Health, Old Road Campus, University of Oxford, Oxford, OX3 7LF, UK

Katie Walsh, Foundation Doctor, Health Economics Research Centre, Nuffield Department of Population Health, Old Road Campus, University of Oxford, Oxford, OX3 7LF, UK

Isaac Ghinai, Academic Clinical Fellow, Health Economics Research Centre, Nuffield Department of Population Health, Old Road Campus, University of Oxford, Oxford, OX3 7LF, UK

Seher Mughal, Health Economics Research Centre, Nuffield Department of Population Health, Old Road Campus, University of Oxford, Oxford, OX3 7LF, UK

Elsbeth Nye, Foundation Doctor, Health Economics Research Centre, Nuffield Department of Population Health, Old Road Campus, University of Oxford, Oxford, OX3 7LF, UK

Helena Wace, Foundation Doctor, Health Economics Research Centre, Nuffield Department of Population Health, Old Road Campus, University of Oxford, Oxford, OX3 7LF, UK

Nia Roberts, Information Specialist, Bodleian Health Care Libraries, Old Road Campus, University of Oxford, Oxford, OX3 7LF, UK

Pascal Lecomte, Global Head Health Economic Modelling and Methodology, Novartis Pharma AG, 4002 Basel, Switzerland

Raphael Wittenberg, Associate Professorial Research Fellow, Personal Social Services Research Unit, London School of Economics and Political Science, Houghton Street, London WC2A 2AE, UK

Jane Wolstenholme, Senior Health Economist, Health Economics Research Centre, Nuffield Department of Population Health, Old Road Campus, University of Oxford, Oxford, OX3 7LF, UK

Ron Handels, Researcher, Alzheimer Centre Limburg, Department of Psychiatry and Neuropsychology, School for Mental Health and Neurosciences, Maastricht University, Maastricht, The Netherlands, and Department of Neurobiology, Care Science and Society, Division of Neurogeriatrics, Karolinska Institute, Stockholm, Sweden

Emilse Roncancio-Diaz, Health Economics and Outcomes Research Manager, Life Sciences, GE Healthcare, White Lion Rd, Little Chalfont, Amersham HP7 9LL, UK

Michele H. Potashman, Associate Director, Value and Access, Biogen, 225 Binney St, Cambridge MA 02139, USA

Antje Tockhorn-Heidenreich, Senior Research Scientist, Eli Lilly and Company, Erl Wood Manor, Windlesham, GU20 6PH, UK

Alastair M. Gray, Professor of Health Economics, Health Economics Research Centre, Nuffield Department of Population Health, Old Road Campus, University of Oxford, Oxford, OX3 7LF, UK

Correspondence to: Filipa Landeiro filipa.landeiro@dph.ox.ac.uk

Abstract

Introduction: Dementia is the fastest growing major cause of disability globally and may have a profound impact on the health-related quality of life (HRQoL) of both the patient with dementia and those who care for them. This review aims to systematically identify and synthesize the measurements of HRQoL for people with and their caregivers across the full spectrum of dementia, from its preceding stage of pre-dementia to end of life.

Methods and analysis: A systematic literature review was conducted in MEDLINE, Embase, CDSR, CENTRAL, DARE, NHS EED, and PsycINFO between January 1990 and the end of April 2017. Two reviewers will independently assess each study for inclusion and disagreements will be resolved by a third reviewer. Data will be extracted using a pre-defined data extraction form following best practice. Study quality will be assessed with the Effective Public Health Practice Project quality assessment tool. HRQoL measurements will be presented separately for people with dementia and caregivers by instrument used and, when possible, HRQoL will be reported by disease type and stage of the disease. Descriptive statistics of the results will be provided. A narrative synthesis of studies will also be provided discussing differences in HRQoL measurements by instrument used to estimate it, type of dementia and disease severity.

Ethics and Dissemination: This systematic literature review is exempt from ethics approval because the work is carried out on published documents. The findings of the review will be disseminated in a related peer-reviewed journal and presented at conferences. They will also contribute to the work developed in the Real World Outcomes across the Alzheimer's disease spectrum for better care: multi-modal data access platform (ROADMAP).

Trial registration number: CRD42017071416

Keywords: dementia, Alzheimer's disease, patient, caregiver, carer, quality of life, systematic review, utility

Strengths of study

- This systematic literature review on quality of life of people with pre-dementia and dementia and their caregivers is based on a detailed search strategy including studies from any country published in any language, covering the time frame from 1st January 1990 until 28th April 2017.
- The review follows robust guidelines and the quality of the papers included will be assessed using a validated tool.

Limitations of study

- The heterogeneity in the way quality of life is measured and reported may not allow for direct comparisons between studies.

Introduction

Dementia is a global disease with little prospect of a cure or means of preventing its progression. In 2014, it was estimated to affect 7.1% of people aged 65 and above worldwide[1]. It is a debilitating neurodegenerative condition which causes a progressive and irreversible decline in cognitive, social and physical function. There are several types of dementia and some people may present with a combination of types. Alzheimer's disease (AD) is the most common cause of dementia, accounting for 60-80% of all cases[2]. Other causes include vascular dementia (VaD), frontotemporal dementia (FTD), dementia with Lewy bodies (DLB) and others. Irrespective of the cause, dementia results in significant decline in intellectual abilities, such as memory, and causes behavioural changes, insight and judgement, anxiety and depression, with eventual loss of physical functions and personality. This eventually becomes severe enough to interfere with a person's daily functioning and activities of daily living (ADLs).

The cognitive and functional decline associated with dementia has a profound impact on the health-related quality of life (HRQoL) of both the patient and those that care for them. HRQoL, defined as the way health is empirically estimated to affect QoL, is a multi-dimensional concept that includes domains related to physical, mental, emotional and social functioning. HRQoL is now recognised as an increasingly valued health outcome measure in dementia. With no cure, the focus of attention in dementia care is to promote patient well-being and to maintain optimal HRQoL. As HRQoL refers to all aspects of a person's life it can provide valuable information on the patient's self-perception of health and intervention impact. HRQoL measures attempt to evaluate directly the impact of dementia or interventions on people's ability to function in life. They have therefore become a key way in which to assess the effectiveness of health and social service interventions.

Dementia patients require long term care and support and the responsibility for caregiving most often falls upon informal caregivers including family members, friends and neighbours. These caregivers provide a valuable resource for dementia patients. There are over 700,000 informal caregivers of people with dementia estimated to be providing £12.4 billion of unpaid care in the UK per year[3]. The work of these caregivers is vital to support the growing number of people affected by dementia and without them the formal care system would likely collapse. The National Dementia Strategy for England[4] recognises this and supporting caregivers is now a national and international policy priority[5].

Given that caregivers of people with dementia are considered to be such an important resource, it is important to ensure that their own HRQoL is satisfactory. For many, the experience of caring for their loved ones provides personal satisfaction. However, the experience can also have a negative impact. Caregivers often have high levels of anxiety, stress and depression[6] as caring for people with dementia often places a heavy mental, physical, financial, and social burden on them[7-11]. Great demands are placed on caregivers who are often elderly themselves[8 9]. As a result caregivers might find themselves neglecting their own health and HRQoL. This could ultimately impact on the quality of the care that they provide for people with dementia. Therefore, addressing caregivers' HRQoL is an important challenge.

Shearer et al.[10] conducted a systematic review of the literature on health value states for AD patients and their caregivers based on generic preference-based instruments[10]. Two recently published systematic reviews examined the factors associated with the HRQoL of dementia patients, either in all types of setting[12] or in long-term care facilities in particular[13]. A few reviews have identified HRQoL measures for dementia patients and their carers[14-16]. Caregiver burden has also been explored in a few systematic reviews, either identifying factors constituting caregiver burden on informal caregivers of dementia patients[7], exploring the role of self-efficacy in HRQoL of family carers of dementia patients[8], reviewing evidence for negative caregiver outcomes in mild cognitive impairment (MCI)[9] and synthesising risk factors, or reviewing caregiver burden and interventions for familial caregivers of AD's patients[11]. However, apart from Shearer et al.[10], none of these reviews report measurements for HRQoL of these patients or caregivers. Furthermore, Shearer et al.[10] did not consider dementia-specific HRQoL measures. This review therefore aims to address this gap in the literature by addressing the following questions:

1. What is the HRQoL for people with dementia across all stages of disease severity, from its preceding state of pre-dementia (including pre-clinical AD – biomarker positive but pre-symptomatic, early symptoms, MCI, or prodromal AD), through to diagnosed dementia and end of life?
2. What is the HRQoL for caregivers of people with dementia across all stages of disease severity, from its preceding stage of pre-dementia to end of life?

Methods and analysis

Protocol and registration

The preparation of this protocol followed the reporting guidelines of the Preferred Reporting Items for Systematic Reviews and Meta-Analysis for Protocols 2015 (PRISMA-P)[17]. A completed PRISMA-P checklist is available in Supplementary file 1. The protocol was registered with the PROSPERO international prospective register of systematic reviews (registration number CRD42017071416). The systematic review manuscript will be prepared following the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) statement[18-20]. In case of amendments to this protocol, they will be reported and published with the results of the review.

Study selection criteria

Participants

The focus of this review is on adult populations reporting to have either pre-dementia or dementia, irrespective of the type and stage of the disease, and their caregivers. Our main interest is in AD, the most common cause of dementia, but given the lack of diagnostic accuracy and the recognised overlap between different causes of dementia, all causes will be considered.

Study design

This systematic literature review will include studies reporting measurements of HRQoL for adult-onset pre-dementia or dementia patients and their caregivers published in peer-reviewed journals or grey literarure. We will only include primary studies that provide quantitative results. Qualitative studies will not be included.

The following study designs will be considered for inclusion: experimental studies, quasi-experimental studies, observational studies (either prospective or retrospective) and register-based studies. In cases where multiple studies used the same patient cohort, we will use the data from the study that presented the most detailed information on HRQoL. Case-studies, series of case-studies, studies with sample size of 30 or less patients, trial protocols, phase I clinical trials, news articles, interviews that do not use a structured quantitative questionnaire, patient education handouts, reviews, opinion or expert articles, editorials, letters to the editor, authors and editor's replies to comments will not be included.

Modelling studies will be excluded but studies informing the model parameters will be considered for inclusion. Similarly, existing reviews of HRQoL of people with dementia and their caregivers will not be included but their reference lists will be screened for additional studies. Conference abstracts will not be included. However, the abstracts will be screened to determine whether the work presented has been published in a peer-reviewed journal or thesis. If this is the case, then the published study will be considered for inclusion.

Outcomes

The outcomes of interest are:

- The HRQoL of people with either pre-dementia or dementia;
- The HRQoL of caregivers of people with either pre-dementia or dementia.

Where possible, the HRQoL of people with dementia and their caregivers will be detailed by stage of the disease: pre-clinical dementia (biomarker positive but pre-symptomatic), early symptoms (memory and other behavioural changes), MCI, prodromal AD, mild dementia, moderate dementia, severe dementia and end of life, in order to understand how HRQoL evolves throughout disease progression.

Quality of life

A wide range of instruments have been developed to measure HRQoL. These include both generic and disease-specific instruments. Whereas generic HRQoL measures are universal and cover general health aspects, regardless of the presence of absence of a disease, disease-specific HRQoL measures target individual diseases and aim to emphasise the problems specific to patients with a specific disease, such as dementia. These generic and disease-specific instruments can be further subdivided into preference or non-preference depending on whether the index has been derived by using preference weights obtained from patients or the general public, or using simple summation of item scores.

In this review we will include any study reporting a quantitative measurement of HRQoL, regardless of the instrument used to estimate it.

Intervention

All types of interventions related to dementia, either symptomatic or disease modifying, will be included. We will also include studies that have not assessed any intervention.

Language

No language restrictions were applied to the search.

Setting

No geography restrictions were applied to the search.

Search strategy

Electronic databases

The selection of the electronic databases used was carried out with the assistance of an information specialist. The search terms were devised in conjunction with an information specialist based on the search strategy of a previous literature review[10]. Medical Literature Analysis and Retrieval System Online (MEDLINE), Excerpta Medica dataBASE (Embase), Cochrane Database of Systematic Reviews (CDSR), Central Register of Controlled Trials (CENTRAL), Database of Abstracts of Reviews of Effects (DARE), NHS Economic Evaluation Database (NHS EED), and PsycINFO were searched for studies published between 1st January 1990 and 28th April 2017. Supplementary file 2 provides a description of the search terms used in each database.

Manual searches

The reference list of the studies included in this review, as well as those of previous literature reviews on HRQoL across the full spectrum of dementia, will be searched in order to identify additional potentially relevant studies. The studies informing the model parameters in identified modelling studies will be considered for inclusion. Conference abstracts identified through the electronic searches will be screened and manuscripts of relevant abstracts will be manually searched for.

Study selection

ENDNOTE X7, Thomson Reuters, will be used for reference management. Database results will be imported to ENDNOTE where duplicates will be removed by one reviewer (KW) based on title and first author name. Subsequently, two reviewers (FL and KW) will independently assess the titles and abstract of the studies to determine whether full text review is needed, with disagreement being resolved by a third reviewer (HW). Full text will be sought for potentially relevant studies and assessed for final inclusion by two reviewers (FL and KW) with disagreements being resolved by a third reviewer (HW). The full selection process will be presented in a flow diagram according to PRISMA guidelines[18].

Data extraction

Two of the following reviewers (SM, EN, FL, AG and JW) will extract the data from the final set of studies onto a data extraction form (Supplementary file 3) with disagreements being solved by a third reviewer. Two native or fluent speakers will review and extract the data for the non-English references. The following information will be extracted:

- Study details: title, author, publication details, language of the study, countries of the study;
- Study design: aim of the study, type of study, type of analysis, duration, outcomes measured, instruments used to measure them, administration mode;
- Participant information: type of participant, setting, inclusion and exclusion criteria, sample size, socio-demographic information, self or proxy-rating;
- Disease specific information: type of dementia, level of severity, instrument used to measure level of severity;
- Outcomes: outcomes measured, time points measured, subgroup analysis conducted;
- Results: HRQoL of patients by disease severity, HRQoL of caregivers by disease severity of the patients (where studies report HRQoL using different instruments or report the same instrument in different ways, data will be extracted for each of them);
- Conclusions: Authors conclusions.

Risk of bias (quality) assessment

The Effective Public Health Practice Project "Quality assessment tool for quantitative studies"[21] recommended by the Cochrane Public Health Group will be used to assess the quality of the studies included in this review as it covers a wide range of study designs[22]. Two of above mentioned reviewers will independently assess each study and two native or fluent speakers will independently assess the quality of each of the non-English studies.

Description of studies and analysis

We expect to find a diverse range of HRQoL measures for both patients and caregivers. The HRQoL measurements will be presented separately for patients and caregivers by instrument used and, if possible, graphically. When described, distinction will be made between the different types of dementia, but with a special emphasis on AD, the most common cause. If possible, HRQoL will be reported for each stage of the disease and if the HRQoL was self-rated or proxy-rated informed by a caregiver or care/research professional. Descriptive statistics of the results will be provided.

A narrative synthesis of all relevant studies will be provided discussing differences in HRQoL measurements by instrument used to estimate it, type of dementia, disease severity, setting and describing study and participants' characteristics, results and author's conclusions.

In case the study does not provide all the necessary data for our analysis, we will contact the authors of the studies included in this review to attempt to retrieve it.

If feasible, a meta-analysis of the findings will be conducted.

Ethics and dissemination

This systematic literature review is exempt from ethical approval because the work will be carried out on published documents. The studies that are included in this review will be examined to determine if ethical issues have been considered. The results of this review will be disseminated in a peer-reviewed journal and presented at conferences, and will also contribute to the Real World Outcomes across the Alzheimer's disease spectrum for better care: multi-modal data access platform (ROADMAP).

Discussion

This systematic literature review will identify and synthesize the measurements of QoL, both preference and non-preference based, for patients across the full spectrum of dementia from MCI, pre-dementia and dementia to end of life, and their caregivers. HRQoL is increasingly seen as an important outcome in dementia research and this level of detailed measurements of HRQoL will be useful and help to better inform disease progression and cost-effectiveness models of dementia.

We will present HRQoL measurements separately by disease type, when the information is available. The main focus of our research is on AD, the most common cause of dementia, but given the lack of diagnostic accuracy and the recognised overlap between different causes of dementia, all causes of dementia will be considered.

Even though HRQoL as a measurement of the health status of individuals has been used since the second half of the 20th century, it was only in the 1990s that its use increased with the introduction of instruments such as EQ-5D-3L[23] and SF-6D[24]. As such, this review will include published studies on HRQoL since 1990. Furthermore, no languages or geographic restrictions were applied to the searches.

In conclusion, the results of this review could inform models assessing interventions on dementia for both patients and their caregivers by providing information about patient's and caregiver's perspective on treatment benefits. Additionally, this synthesis of HRQoL measurements for dementia patients and their caregivers can help policy makers better understand the impact of this staggering clinical condition.

Funding

This project has received funding from the Innovative Medicines Initiative 2 Joint Undertaking under grant agreement No 116020 (“ROADMAP”). This Joint Undertaking receives support from the European Union’s Horizon 2020 research and innovation programme and EFPIA.

Competing interests

FL, KW, IG, SM, EN, HW, NR, RW, JW and AMG declare that they have no competing interests. PL is employed by, owns stock in, and has stock options in Novartis Pharma AG. RH has received consulting fees from Roche, Nutricia and Piramal; research grants from private/public collaborations: IMI2-ROADMAP; Alzheimer Netherlands Flutemetamol; CTMM LEARN Grant 02 N-101; and public grants from: JPND Actifcare; and JPND BIOMARKAPD. ERD is employed by GE Healthcare. MP is an employee of Biogen and owns stock in Biogen. She owns stock in a variety of companies that at times include other pharmaceutical and health care-related companies. ATH is an employee of Eli Lilly and Company Limited and owns stock in Eli Lilly and Company Limited. Novartis Pharma AG, GE Healthcare, Biogen and Eli Lilly and Company Limited are industry partners in the ROADMAP Project.

Contributors

FL designed the study and is the guarantor of the review. FL, KW, IG, SM, EN and HW wrote the protocol. FL, NR, RW, JW, RH, MHP, ATH and AMG devised the search strategy. PL, RW, JW, RH, ERD, MHP, ATH, and AMG critically appraised the protocol and also contributed to its development by revising different versions. All authors read and approved the final version of the manuscript.

Acknowledgments

We would like to acknowledge the contributions of the remaining members of Work Package 5 as well as of those of the wider ROADMAP group.

References

1. Prince M, Knapp M, Guerchet M, et al. Dementia UK: update. Alzheimer’s Society 2014.
2. Association As. 2017 Alzheimer's disease facts and figures. Alzheimer's & Dementia 2017;**13**(4):325-73.
3. Lewis F, Karlsberg Schaffer S, Sussex J, et al. The trajectory of dementia in the UK—Making a difference. OHE Consulting 2014.
4. Banerjee S, Owen J. Living well with dementia: a national dementia strategy. London: Department of Health 2009.
5. International; WHOAsD. Dementia: a public health priority. In: Organization WH, ed., 2012.
6. Schoenmakers B, Buntinx F, Delepeleire J. Factors determining the impact of care-giving on caregivers of elderly patients with dementia. A systematic literature review. Maturitas 2010;**66**(2):191-200.
7. Chiao CY, Wu HS, Hsiao CY. Caregiver burden for informal caregivers of patients with dementia: A systematic review. International nursing review 2015;**62**(3):340-50.
8. Crellin NE, Orrell M, McDermott O, et al. Self-efficacy and health-related quality of life in family carers of people with dementia: a systematic review. Aging Ment Health 2014;**18**(8):954-69.
9. Seeher K, Low LF, Reppermund S, et al. Predictors and outcomes for caregivers of people with mild cognitive impairment: a systematic literature review. Alzheimer's & dementia : the journal of the Alzheimer's Association 2013;**9**(3):346-55.
10. Shearer J, Green C, Ritchie CW, et al. Health state values for use in the economic evaluation of treatments for Alzheimer's disease. Drugs & aging 2012;**29**(1):31-43.
11. Wennberg A. DC, Streetman-Loy B., Pham H.,. Alzheimer's Patient Familial Caregivers: A Review of Burden and Interventions. Health and Social Work 2015;**40**(4):e162-e69.
12. Jing W, Willis R, Feng Z. Factors influencing quality of life of elderly people with dementia and care implications: A systematic review. Archives of Gerontology and Geriatrics 2016;**66**:23-41.
13. Beerens HC, Zwakhalen SM, Verbeek H, et al. Factors associated with quality of life of people with dementia in long-term care facilities: a systematic review. International journal of nursing studies 2013;**50**(9):1259-70.
14. Aspden T, Bradshaw SA, Playford ED, et al. Quality-of-life measures for use within care homes: a systematic review of their measurement properties. Age and Ageing 2014;**43**(5):596-603.
15. Jones C, Edwards RT, Hounsome B. Health economics research into supporting carers of people with dementia: A systematic review of outcome measures. Health and Quality of Life Outcomes 2012;**10**(1):142.
16. Algar K, Woods RT, Windle G. Measuring the quality of life and well-being of people with dementia: A review of observational measures. Dementia (London, England) 2016;**15**(4):832-57.
17. Shamseer L, Moher D, Clarke M, et al. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015: elaboration and explanation. Bmj 2015;**349**:g7647.
18. Moher D, Liberati A, Tetzlaff J, et al. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. PLoS med 2009;**6**(7):e1000097.
19. Liberati A, Altman DG, Tetzlaff J, et al. The PRISMA statement for reporting systematic

reviews and meta-analyses of studies that evaluate health care interventions: explanation and elaboration. PLoS Med 2009;**6**(7):e1000100.
20. Welch V, Petticrew M, Tugwell P, et al. PRISMA-Equity 2012 extension: reporting guidelines for systematic reviews with a focus on health equity. Revista Panamericana de Salud Pública 2013;**34**(1):60-67.
21. Thomas H. Quality assessment tool for quantitative studies. Effective Public Health Practice Project McMaster University, Toronto 2003.
22. Armijo-Olivo S, Stiles CR, Hagen NA, et al. Assessment of study quality for systematic reviews: a comparison of the Cochrane Collaboration Risk of Bias Tool and the Effective Public Health Practice Project Quality Assessment Tool: methodological research. Journal of evaluation in clinical practice 2012;**18**(1):12-18.
23. EuroQol--a new facility for the measurement of health-related quality of life. Health policy (Amsterdam, Netherlands) 1990;**16**(3):199-208.
24. Brazier J, Usherwood T, Harper R, et al. Deriving a preference-based single index from the UK SF-36 Health Survey. Journal of clinical epidemiology 1998;**51**(11):1115-28.

Supplementary file 1: PRISMA-P checklist

Section and topic	Item No.	Checklist Item	Reported on page #
A) Administrative Information			
Identification	1a	Identify the report as a protocol of a systematic review	1
Update	1b	Identify protocol as an update of a previous systematic review if applicable	n/a
Registration	2	Name of registry and registration number	2
B) Authors			
Contact		Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author	1
Contributions		Describe contributions of protocol authors and identify the guarantor of the review	1 + 12
Amendments		If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments	n/a
Support			
- Sources	5a	Indicate Sources of financial or other support for the review	12
- Sponsor	5b	Provide name for the review funder and/or sponsor	11
- Role of sponsor or funder	5c	Describe roles of funder(s), sponsor(s) and/or institution(s), if any, in developing the protocol	13
C) Introduction			
Rationale	6	Describe the rationale for the review in the context of what is already known	3 + 4
Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	4 + 5
D) Methods			
Eligibility Criteria	8	Specify the study characteristics (such as PICO, study design, setting, time frame) and report characteristics (such as years considered, language, publication status) to be used as criteria for eligibility for the review	5 + 6 + 7
Information Sources	9	Describe all intended information sources (such as electronic databases, contact with study authors, trial registers or other grey literature sources) with planned dates of coverage	7 + 8
Search Strategy	10	Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated	Supplementary file 2
E) Study Records			
Data Management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	8

Selection Process	11b	State the process that will be used for selecting studies (such as two independent reviewers) through each phase of the review (that is, screening, eligibility and inclusion in meta-analysis)	5 - 10
Data Collection Process	11c	Describe planned method of extracting data from reports (such as piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators	8 - 10 + Supplementary file 3
Data Items	12	List and define all variables for which data will be sought (such as PICO items, funding sources), any pre-planned data assumptions and simplifications	8 - 9
Outcomes and prioritization	13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	6 + 9
Section and topic	**Item No.**	**Checklist Item**	**Reported on page #**
Risk of bias in individual studies	14	Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis	9
Data Synthesis	15a	Describe criteria under which study data will be quantitatively synthesised	9 + 10
	15b	If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data and methods of combining data from studies, including any planned exploration of consistency	10
	15c	Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression)	10
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned	9 – 10
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies)	n.a.
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed	9 – 10

Supplementary file 2: Search terms

Medline

# ▲	Searches	Results
1	*dementia/ or *alzheimer disease/ or exp *dementia, vascular/ or exp *frontotemporal lobar degeneration/	98,731
2	*Cognitive Dysfunction/	4,368
3	(dementia* or alzheimer*).ti.	92,750
4	((mild* or early* or preclinical or pre-clinical) adj2 (cognitive impair* or cognitive dysfunction or cognitive decline)).ti.	5,582
5	1 or 2 or 3 or 4	118,970
6	*"Quality of Life"/	69,834
7	("quality of life" or "quality of wellbeing" or "quality of well-being").ti.	55,455
8	(qol or hqol or hrqol or hrql or hr-qol or hr-ql or euroqol or euro qol or eq5d or eq-5d or eq-vas or vas or whoqol or who qol or reqol*).ti,ab.	81,919
9	(sf6 or sf6d or sf12 or sf16 or sf20 or sf36).ti,ab.	2,656
10	((sf or shortform or short-form) adj ("6" or 6d or "12" or "16" or "20" or "36" or six or twelve or sixteen or twenty or thirtysix or thirty six)).ti,ab.	26,238
11	(icepop or icecap* or duke health profile or dhp or core outcome measure? or core om).ti,ab.	2,772
12	(aaiqol or aai-qol or cdqlp or qolas or qolad or qol-ad or qold or dqol or demqol or adrql or adrqol or oqold or oqolda or seiqol or rsoc-qol or qualid or qualidem or qwb-sa or hsq-12 or zbi or zarit or ces-d or "activity and affect indicator*" or dcm or pwbcip or pwb-cip or npi-d or ham-d or basquid or basqid or stai or stai-5 or bdi or gds or gps or hui or hui-ii or hui-iii or isd or pds or pes-ad or pesad or pes-ad-aes or pesadaes or ghq or cas or cbs or qwb or cbi or bsi or srb or phq-9).ti,ab.	82,505
13	(modified coop* or modified wonca* or "psychological well-being in cognitively impaired persons").ti,ab.	23
14	*Personal Satisfaction/ or *Patient Satisfaction/	31,894
15	((life or patient* or carer? or caregiver? or spous* or wife or wives or husband?) adj satisfaction).ti.	7,129
16	((life or patient* or carer? or caregiver? or spous* or wife or wives or husband?) adj (experience? or preference? or perspective?)).ti.	8,647
17	(wellbeing or well-being).ti.	11,493
18	((life or patient* or carer? or caregiver? or spous* or wife or wives or husband?) adj (experience? or preference? or perspective?)).ti.	8,647
19	caregiver time.ti,ab.	140
20	14 or 15 or 16 or 17 or 18 or 19	51,145
21	"surveys and questionnaires"/ or self report/	394,101
22	(questionnaire? or survey?).ti,ab.	804,666
23	self report.ti,ab.	42,432
24	((patient* or carer? or caregiver? or spous* or wife or wives or husband? or proxy) adj report?).ti,ab.	7,095
25	21 or 22 or 23 or 24	976,414

26	20 and 25	23,719
27	*Caregivers/ and *"Cost of Illness"/	1,619
28	((carer? or caregiver? or care or spous* or wife or wives or husband?) adj2 (burden* or cost?)).ti.	5,142
29	burden interview?.ti.	50
30	"value of life".ti.	87
31	*"Activities of Daily Living"/	17,986
32	("activities of daily living" or acdl or funtional status).ti.	1,772
33	*quality-adjusted life years/	1,917
34	("quality adjusted life years" or "disability adjusted life years" or qaly? or daly? or qald or qale or qtime or qualy).ti.	764
35	*Health Status/	34,353
36	*sickness impact profile/	2,623
37	(standard gamble or "time trade off" or utility index or visual analog*).ti,ab.	48,455
38	(health utilit* or disutilit* or utility value?).ti,ab.	2,889
39	health status.ti.	9,145
40	6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 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	322,206
41	5 and 40	4,530
42	limit 41 to yr="1990 -Current"	4,445
43	(case reports or clinical trial phase i or comment or editorial or letter).pt. or Clinical Trials, Phase I as Topic/ or (case report or case study or letter? or editorial).ti.	3,400,815
44	grounded theory/ or exp qualitative research/ or (qualitative research or qualitative study or qualitative interview* or grounded theory or hermeneutic*).ti,ab.	67,630
45	43 or 44	3,466,599
46	42 not 45	4,087

Embase

# ▲	Searches	Results
1	exp *dementia/ or *alzheimer's disease/	177,994
2	*cognitive impairment/	40,861
3	(dementia* or alzheimer*).ti.	119,362
4	((mild* or early* or preclinical or pre-clinical) adj2 (cognitive impair* or cognitive dysfunction or cognitive decline)).ti.	8,090
5	1 or 2 or 3 or 4	223,452
6	exp *"quality of life"/	80,143
7	("quality of life" or "quality of wellbeing" or "quality of well-being").ti.	76,232
8	(qol or hqol or hrqol or hrql or hr-qol or hr-ql or euroqol or euro qol or eq5d or eq-5d or eq-vas or vas or whoqol or who qol or reqol*).ti,ab.	129,834
9	(sf6 or sf6d or sf12 or sf16 or sf20 or sf36).ti,ab.	4,872

10	((sf or shortform or short-form) adj ("6" or 6d or "12" or "16" or "20" or "36" or six or twelve or sixteen or twenty or thirtysix or thirty six)).ti,ab.	37,206
11	(icepop or icecap* or duke health profile or dhp or core outcome measure? or core om).ti,ab.	3,316
12	(aaiqol or aai-qol or cdqlp or qolas or qolad or qol-ad or qold or dqol or demqol or adrql or adrqol or oqold or oqolda or seiqol or rsoc-qol or qualid or qualidem or qwb-sa or hsq-12 or zbi or zarit or ces-d or "activity and affect indicator*" or dcm or pwbcip or pwb-cip or npi-d or ham-d or basquid or basqid or stai or stai-5 or bdi or gds or gps or hui or hui-ii or hui-iii or isd or pds or pes-ad or pesad or pes-ad-aes or pesadaes or ghq or cas or cbs or qwb or cbi or bsi or srb or phq-9).ti,ab.	114,337
13	(modified coop* or modified wonca* or "psychological well-being in cognitively impaired persons").ti,ab.	29
14	*client satisfaction/ or *life satisfaction/	1,991
15	((life or patient* or carer? or caregiver? or spous* or wife or wives or husband?) adj satisfaction).ti.	8,839
16	((life or patient* or carer? or caregiver? or spous* or wife or wives or husband?) adj (experience? or preference? or perspective?)).ti.	11,228
17	(wellbeing or well-being).ti.	12,234
18	((life or patient* or carer? or caregiver? or spous* or wife or wives or husband?) adj (experience? or preference? or perspective?)).ti.	11,228
19	caregiver time.ti,ab.	183
20	14 or 15 or 16 or 17 or 18 or 19	33,365
21	"surveys and questionnaires"/ or self report/	582,726
22	(questionnaire? or survey?).ti,ab.	1,011,521
23	self report.ti,ab.	50,950
24	((patient* or carer? or caregiver? or spous* or wife or wives or husband? or proxy) adj report?).ti,ab.	10,383
25	21 or 22 or 23 or 24	1,187,376
26	20 and 25	14,705
27	*caregiver burden/	1,934
28	((carer? or caregiver? or care or spous* or wife or wives or husband?) adj2 (burden* or cost?)).ti.	6,435
29	burden interview?.ti.	59
30	"value of life".ti.	96
31	*"activities of daily living"/	8,385
32	("activities of daily living" or acdl or funtional status).ti.	2,164
33	*quality adjusted life year/	1,084
34	("quality adjusted life years" or "disability adjusted life years" or qaly? or daly? or qald or qale or qtime or qualy).ti.	898
35	*Health Status/	28,930
36	*sickness impact profile/	689
37	(standard gamble or "time trade off" or utility index or visual analog*).ti,ab.	64,774
38	(health utilit* or disutilit* or utility value?).ti,ab.	4,516
39	health status.ti.	9,969
40	6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 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	393,955

41	5 and 40	6,763
42	limit 41 to yr="1990 -Current"	6,613
43	(editorial or letter or note or press).pt. or "phase 1 clinical trial (topic)"/ or case report/ or (case report or case study or letter? or editorial).ti.	4,421,368
44	grounded theory/ or exp qualitative research/ or (qualitative research or qualitative study or qualitative interview* or grounded theory or hermeneutic*).ti,ab.	71,138
45	43 or 44	4,489,168
46	42 not 45	6,122

PsycINFO

# ▲	Searches	Results
1	exp *dementia/ or *alzheimer's disease/	58,737
2	*cognitive impairment/	23,977
3	(dementia* or alzheimer*).ti.	47,312
4	((mild* or early* or preclinical or pre-clinical) adj2 (cognitive impair* or cognitive dysfunction or cognitive decline)).ti.	3,675
5	1 or 2 or 3 or 4	77,854
6	exp *"quality of life"/	28,944
7	("quality of life" or "quality of wellbeing" or "quality of well-being").ti.	17,544
8	(qol or hqol or hrqol or hrql or hr-qol or hr-ql or euroqol or euro qol or eq5d or eq-5d or eq-vas or vas or whoqol or who qol or reqol*).ti,ab.	15,758
9	(sf6 or sf6d or sf12 or sf16 or sf20 or sf36).ti,ab.	243
10	((sf or shortform or short-form) adj ("6" or 6d or "12" or "16" or "20" or "36" or six or twelve or sixteen or twenty or thirtysix or thirty six)).ti,ab.	5,546
11	(icepop or icecap* or duke health profile or dhp or core outcome measure? or core om).ti,ab.	367
12	(aaiqol or aai-qol or cdqlp or qolas or qolad or qol-ad or qold or dqol or demqol or adrql or adrqol or oqold or oqolda or seiqol or rsoc-qol or qualid or qualidem or qwb-sa or hsq-12 or zbi or zarit or ces-d or "activity and affect indicator*" or dcm or pwbcip or pwb-cip or npi-d or ham-d or basquid or basqid or stai or stai-5 or bdi or gds or gps or hui or hui-ii or hui-iii or isd or pds or pes-ad or pesad or pes-ad-aes or pesadaes or ghq or cas or cbs or qwb or cbi or bsi or srb or phq-9).ti,ab.	27,360
13	(modified coop* or modified wonca* or "psychological well-being in cognitively impaired persons").ti,ab.	14
14	*client satisfaction/ or *life satisfaction/	10,500
15	((life or patient* or carer? or caregiver? or spous* or wife or wives or husband?) adj satisfaction).ti.	4,378
16	((life or patient* or carer? or caregiver? or spous* or wife or wives or husband?) adj (experience? or preference? or perspective?)).ti.	3,089
17	(wellbeing or well-being).ti.	17,565
18	((life or patient* or carer? or caregiver? or spous* or wife or wives or husband?) adj (experience? or preference? or perspective?)).ti.	3,089
19	caregiver time.ti,ab.	51

20	14 or 15 or 16 or 17 or 18 or 19	30,716
21	questionnaires/ or surveys/ or self report/	36,535
22	(questionnaire? or survey?).ti,ab.	409,092
23	self report.ti,ab.	49,405
24	((patient* or carer? or caregiver? or spous* or wife or wives or husband? or proxy) adj report?).ti,ab.	2,724
25	21 or 22 or 23 or 24	446,678
26	20 and 25	10,093
27	*caregiver burden/	4,122
28	((carer? or caregiver? or care or spous* or wife or wives or husband?) adj2 (burden* or cost?)).ti.	1,257
29	burden interview?.ti.	42
30	"value of life".ti.	33
31	*"activities of daily living"/	3,835
32	("activities of daily living" or acdl or funtional status).ti.	734
33	("quality adjusted life years" or "disability adjusted life years" or qaly? or daly? or qald or qale or qtime or qualy).ti.	142
34	(standard gamble or "time trade off" or utility index or visual analog*).ti,ab.	6,195
35	(health utilit* or disutilit* or utility value?).ti,ab.	877
36	health status.ti.	2,312
37	6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35 or 36	85,145
38	5 and 37	4,392
39	limit 38 to yr="1990 -Current"	4,344
40	case report/ or (case report or case study or letter? or editorial).ti.	62,005
41	grounded theory/ or qualitative research/ or (qualitative research or qualitative study or qualitative interview* or grounded theory or hermeneutic*).ti,ab.	61,499
42	40 or 41	122,316
43	39 not 42	4,208

Cochrane Database of Systematic Reviews, Cochrane Central Register of Controlled Trials, Database Abstract of Reviews of Effects, NHS Economic Evaluation Database

ID	Search
#1	MeSH descriptor: [Dementia] explode all trees
#2	MeSH descriptor: [Mild Cognitive Impairment] explode all trees
#3	dementia* or alzheimer*:ti (Word variations have been searched)
#4	((mild* or early* or preclinical or pre-clinical) near/2 (cognitive impair* or cognitive dysfunction or cognitive decline)):ti (Word variations have been searched)
#5	#1 or #2 or #3 or #4
#6	MeSH descriptor: [Quality of Life] explode all trees
#7	quality of life or "quality of wellbeing" or "quality of well-being":ti (Word variations have been searched)
#8	qol or hqol or hrqol or hrql or hr-qol or hr-ql or euroqol or euro qol or eq5d or eq-5d or eq-vas or vas or whoqol or who qol or reqol*:ti,ab,kw (Word variations have been searched)

#9	sf6 or sf6d or sf12 or sf16 or sf20 or sf36:ti,ab,kw (Word variations have been searched)
#10	((sf or shortform or short-form) next ("6" or 6d or "12" or "16" or "20" or "36" or six or twelve or sixteen or twenty or thirtysix or thirty six)):ti,ab,kw (Word variations have been searched)
#11	icepop or icecap* or "duke health profile" or dhp or "core outcome measure?" or "core om":ti,ab,kw (Word variations have been searched)
#12	aaiqol or aai-qol or cdqlp or qolas or qolad or qol-ad or qold or dqol or demqol or adrql or adrqol or oqold or oqolda or seiqol or rsoc-qol or qualid or qualidem or qwb-sa or hsq-12 or zbi or zarit or ces-d or "activity and affect indicator*" or dcm or pwbcip or pwb-cip or npi-d or ham-d or basquid or basqid or stai or stai-5 or bdi or gds or gps or hui or hui-ii or hui-iii or isd or pds or pes-ad or pesad or pes-ad-aes or pesadaes or ghq or cas or cbs or qwb or cbi or bsi or srb or phq-9:ti,ab,kw (Word variations have been searched)
#13	modified coop* or "modified wonca*" or "psychological well-being in cognitively impaired persons":ti,ab,kw (Word variations have been searched)
#14	MeSH descriptor: [Patient Satisfaction] this term only
#15	MeSH descriptor: [Personal Satisfaction] explode all trees
#16	((life or patient* or carer? or caregiver? or spous* or wife or wives or husband?) next satisfaction):ti,ab,kw (Word variations have been searched)
#17	((life or patient* or carer? or caregiver? or spous* or wife or wives or husband?) next (experience? or preference? or perspective?)):ti,ab,kw (Word variations have been searched)
#18	wellbeing or well-being:ti (Word variations have been searched)
#19	((life or patient* or carer? or caregiver? or spous* or wife or wives or husband?) next (experience? or preference? or perspective?)):ti,ab,kw (Word variations have been searched)
#20	caregiver time:ti,ab,kw (Word variations have been searched)
#21	((carer? or caregiver? or care or spous* or wife or wives or husband?) near/2 (burden* or cost?)):ti,ab,kw (Word variations have been searched)
#22	burden interview?:ti,ab,kw (Word variations have been searched)
#23	value of life:ti,ab,kw (Word variations have been searched)
#24	MeSH descriptor: [Activities of Daily Living] explode all trees
#25	activities of daily living or acdl or "funtional status":ti,ab,kw (Word variations have been searched)
#26	MeSH descriptor: [Quality-Adjusted Life Years] explode all trees
#27	quality adjusted life years or "disability adjusted life years" or qaly? or daly? or qald or qale or qtime or qualy:ti,ab,kw (Word variations have been searched)
#28	MeSH descriptor: [Health Status] this term only
#29	MeSH descriptor: [Sickness Impact Profile] explode all trees
#30	standard gamble or "time trade off" or "utility index" or "visual analog*":ti,ab,kw (Word variations have been searched)
#31	health utilit* or disutilit* or "utility value?":ti,ab,kw (Word variations have been searched)
#32	HEALTH STATUS:ti (Word variations have been searched)
#33	#6 or #7 or #8 or #9 or #10 or #11 or #12 or #13 or #14 or #15 or #16 or #17 or #18 or #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
#34	#5 and #33

Supplementary file 3: Data extraction form

QoL Data Extraction Form

Study ID *(surname of first author and year first full report of study was published e.g. Smith 2001)*	
Publication Title	
Notes:	

General Information

Date when form was completed *(dd/mm/yyy)*	
Name of person extracting data	
Language of study	
Corresponding author contact details	
Publication type (e.g. full report, abstract, letter)	
Notes:	

Study Design

	Descriptions as stated in the study	
Aim of the study		
Type of study	Interventional study:	
	Randomised controlled trial	☐
	Non-randomised controlled trial	☐
	Cross-over randomised controlled trial	☐
	Before-and-after study	☐
	Observational study:	
	Case-control study	☐
	Cohort study	☐
	Cross-sectional study	☐
	Other (specify):	
	Register based study	☐
	Other design (specify):	
Type of analysis	Prospective	☐
	Retrospective	☐
	Unclear	☐
QoL instrument(s)		

QoL instrument language	
QoL instrument mode of administration (e.g. paper copy; electronic; telephone; face-to-face interview)	
Outcomes measured other than QoL?	
Start date	
End date	
Follow up (in months)	
Ethical approval needed/ obtained for study	☐ Yes ☐ No ☐ Unclear

Participants

	Description as stated in paper/report
Country (ies)	
Population Description	
Type of Participant	Patients ☐ Caregivers ☐ Other: …………………………………….. ☐
Setting	Community ☐ Institutional ☐ Primary Care ☐ Secondary Care ☐ Tertiary Care ☐ Mixed ☐ Unclear ☐ Other: ………………………….. ☐
Enrolment Eligibility A. Inclusion Criteria B. Exclusion Criteria	A. B.
Recruitment Process	
Sample Size	
Mean age of patients	
Patients gender (% of females in the sample)	
Mean age of caregiver	
Caregiver gender (% of females in the sample)	
Caregiver relationship to patient	Spouse _____% Daughter/son-in-law _____% Daughter _____% Grandchild _____%

	Son _____% Friend _____% Brother _____% Other: _______________ and _____% Sister _____%
Any other relevant sociodemographic information	
Notes:	

Dementia Diagnosis

	Description as stated in paper/report
Type of Dementia	Alzheimer's Disease ☐ Lewy Body Dementia ☐ Vascular Dementia ☐ Mixed ☐ Other: …………………………………… ☐
Disease Severity	Pre-clinical dementia ☐ Early symptoms ☐ MCI ☐ Prodromal AD ☐ Mild dementia ☐ Moderate dementia ☐ Severe dementia ☐ End of Life ☐
Assessment of Disease Severity	Tool Used: ………………………………. Details:
Notes	

Interventions

	Description as stated in paper/report	
Type of Intervention		
Timing of Intervention		
Duration of Intervention Period		
No. of people in each group	Comparison Group	Intervention Group
Implementation		

Outcomes

	Description as stated in paper/report
Outcome Measure	

Time Points Measured	Single Time Point Only ☐ Baseline ☐ Follow Up – Details: ………………………… ☐
Group Measured	Patient ☐ Caregiver ☐
Source *(who the information on outcome measured is obtained from)*	Patient ☐ Caregiver ☐ Clinician ☐ General public ☐ Other: ……………………………………… ☐
Tool Used	
Details	Score Range: …………………
Outcome tool validated	Yes ☐ No ☐ Unclear ☐
Notes	

Results

	Description as stated in paper/report								
Results	Pre-clinical	Early symptoms	MCI	Prodromal AD	Mild dementia	Moderate dementia	Severe dementia	End of Life	Total
Patients' QoL: A. Baseline B. Follow-up									
Caregivers' QoL: A. Baseline B. Follow-up									
Comparison Group:	Baseline	Follow Up	Effect Size	95% CIs					
Intervention Group	Baseline	Follow Up	Effect Size	95% CIs					
Statistical Analysis									
Conclusion									
Any other results reported?									

Conclusions

	Description as stated in paper/report
Author's conclusions	
Reviewer's conclusions	
Correspondence required for further study information *(from whom, what and when)*	
Notes	