**Supplementary file**

## Supplement 1: Details on search strategies, inclusion and exclusion criteria, data extracted and quality appraisal

The following databases were searched for articles published between 2007 and November 2017: CINAHL, MEDLINE, SocScience, EconLit, Elsevier Science Direct. The following subject headings and keywords were used: outcome-related term (i.e. outcome OR benefit OR effect OR endpoint) AND country-related term (i.e. Germany OR Netherlands OR England) AND a technology assessment-related term (i.e. benefit assessment OR technology assessment). If the number of results was particularly large, we added an additional search term for decision making process (i.e. process OR decision making).

In addition, the smart search (CINAHL), recommendations based on previously read articles (Elsevier Direct) and articles frequently cited together (PubMed) functions of databases were used. Additional searches in journals of particular relevance such as 'Value in Health' and 'Medical Decision Making' were also carried out. A few reference searches for key articles were carried out to test if all relevant articles were captured in the searches.

Articles were included that referred to decisions, processes and standards of health technology assessments if they made reference to the role of outcomes. Excluded were articles, which were critical discussions about the use of specific methods - such as: the quality-adjusted life years (QALY) measure; social discount rates in economic evaluation methods; multi-criteria decision making – or which related to personalised medicine, described the influence of HTA processes on market access to drugs or focused on price setting mechanisms and negotiations.

The following information was extracted for each study: study ID; setting; purpose; design; type of data and analysis method; further details about methods (where required); results; conclusions and limitations stated by author(s). For each study a rating was generated to reflect its relevance for our research questions.

In a next step, information was summarised for each country using the following headings (which were identified during the initial analysis of information):

- Responsibilities of HTA and other relevant agencies in regards to HTA or reimbursement process;
- HTA process and requirements;
- Decision making process and criteria;
- Price negotiations and status of listing decision;
- Stakeholder involvement in process;
- Surrogate and composite outcomes;
- Quality of life (and quality-adjusted life years);
- Cost-effectiveness;
- Sub groups.

## Supplement 2: Case study framework and data extraction form

**Case study framework**

Case studies were carried out for health technology assessments / appraisals (HTA) carried out in the dementia/ AD field in three countries: England, Germany and Netherlands.

For England the case study referred to one Multiple Technology Appraisal for donepezil, galantamine, rivastigmine and memantine for the treatment of Alzheimer's disease (AD)[1], which was published 23 March 2011 with last update 11 May 2016. Relevant publicly available documents were included to inform the case studies, such as:

- Guidance and appendices;
- Research recommendations information;
- Documents produced as part of the guidance development such as:
  - Background information (includes review decision documents, press releases);
  - Assessment report documents;
  - Draft and final protocol documents;
  - Draft and final matrix documents;
  - Draft and final scope documents (including consultation comments);
  - Appraisal consultation documents (e.g. Assessment reports; Consultee and commentator comments on the assessment report; Manufacturer and Non-manufacturer Submissions; Expert written personal statements;
  - Final appraisal determination documents (including comments on appraisal consultation

In Germany case studies referred to the following 3 single drug benefit assessments: Memantine in AD; Cholinesterase inhibitors in AD; Ginkgo compounds. There were no technology appraisals in form of early benefit assessments carried out for dementia/ AD drugs since introduction of the new legislation (AMNOG) in 2011. Instead, all appraisals refer to drug assessments carried out before AMNOG. Relevant information included the following documents from the IQWiG website:

- Final and preliminary reports
- Documentation and appraisal of comments on the preliminary report
- Report plan (different versions) and amendments
- Documentation and appraisal of comments on the report plan
- Executive summary of the working paper 'Memantine in Alzheimer's disease: Results of the unpublished studies IE2101 and MEM-MD-22 as well as unpublished responder analyses'
- Press releases

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[1] https://www.nice.org.uk/guidance/ta217

We also looked at the G-BA website for manufacturers' value decisions, G-BA value decisions (Tragende Gruende). Further information about decisions and the role of clinical endpoints in those decisions were also available online[2] [3] [4] [5].

In The Netherlands, case studies referred to short pharmacotherapeutic reports for donezepil (for the indication and symptomatic treatment of mild to moderately severe Alzheimer's dementia)[6]; rivastigmin for people with Parkison's disease and memantine.

Across case studies, the following information were extracted with respect to the following questions:

| Study endpoints (mortality/ morbidity/ quality of life) | Which endpoints were set out during scoping? |
| --- | --- |
| | Which primary endpoints were used in studies that supported the recommendation? (This might include information about categorised clinical endpoints and clinical scales) |
| | Which surrogate endpoints were used that supported recommendations, which methods of validation were used? Did the Committee discuss the appropriateness of surrogate endpoint as validated indicators of endpoints? |
| | How were patient preferences (satisfaction, adherence, complaints) and patient reported outcomes considered? |
| | Which endpoints were considered in cost-effectiveness analysis that supported recommendations? → How was clinical evidence mapped to final endpoint quality of life (in cost-effectiveness analysis)? |
| | Were aspects of meaningful delay and disease progression considered in endpoints? |
| Stakeholder views and influence | Which suggestions were made in regards to clinical endpoints? |
| | Which challenges around including relevant clinical endpoints were discussed by stakeholders? |
| | Were any clinical endpoints were considered differently as a result of stakeholder involvement? |
| | Which clinical endpoints were identified as relevant for future research? |
| Uncertainty | How did uncertainty in data influence discussions about outcome? Were there any criteria or rationales that made an uncertain outcomes more acceptable? |
| Threshold | Which thresholds were applied in regards to clinical measures and/or cost-effectiveness? |
| | How were benefit harm ratios considered? |

**Data extraction form**

[2] https://www.iqwig.de/en/press/press-releases/press-releases/long-struggle-for-appropriately-processed-manufacturer-data-leads-to-a-new-assessment-of-memantine.2216.html
[3] https://www.iqwig.de/en/press/press-releases/press-releases/galantamine-and-rivastigmine-patches-positive-influence-on-cognition-possible.2461.html
[4] https://www.ncbi.nlm.nih.gov/pubmedhealth/PMH0034004/
[5] https://www.ispor.org/News/articles/Oct06/german_policy.asp
[6] https://english.zorginstituutnederland.nl/publications/reports/2013/06/24/donepezil-hydrochloride-aspen-for-the-indication-symptomatic-treatment-of-mild-to-moderately-severe-alzheimer%E2%80%99s-dementia

For each HTA, information was extracted from publicly available documentation relating to the HTA using a range of categories that were derived from headings used in analysis of data from the literature review and from an initial analysis of the information. The categories were as follows:

Outcomes included:

- Outcomes set out during scoping
- Outcomes considered during review
- Outcomes considered differently as a result of stakeholder involvement (Suggestions made by stakeholders in regards to outcomes)
- Outcomes identified as relevant for future research
- Outcomes used in studies that supported the recommendation
- Outcomes considered in cost-effectiveness analysis

Challenges around including outcomes:

- Types of evidence considered
- Surrogate outcomes and methods of validation
- Patient preferences and patient-reported outcomes
- Aspects of meaningful delay and disease progression
- Influence of data uncertainty on outcomes
- Thresholds in regards to outcomes measures or cost-effectiveness

# Supplement 3: Details of studies identified in literature review

| Study ID (Relevance) | Setting | Purpose | Method | Data sources | Details | Results | Limitations |
|---|---|---|---|---|---|---|---|
| **England (N=13)** | | | | | | | |
| **3.1 Allen et al 2017 (Low)** | Australia, Canada, England, Scotland | To compare initial Canadian national HTA recommendations with the initial decisions of the other HTA agencies, and to identify factors for differing national HTA recommendations between the four HTA agencies. | Medicines that were reviewed by all four agencies and received a negative recommendation from only one agency were selected as case studies. Statistical analysis of HTA recommendations classified as positive or negative (numerically coded); percentage agreement was calculated | Information from websites of HTA and bodies responsible for final reimbursement decision | Process map using a previously developed mapping methodology; this enabled identification and relationship between HTA agencies and responsible body for reimbursement decision | HTA bodies considered clinical efficacy; adverse effects; cost-effectiveness; all have implicit or explicit quality-adjusted life-year threshold; factors influencing decisions were: uncertainties surrounding a range of factors including: cost-effectiveness; comparator choice; clinical benefit; safety; trial design; submission timing | Use of publicly available sources; inclusion criteria limited to products listed on Controlled Drug Regulation, which resulted in exclusion of cancer medicines |
| **3.2 Carroll et al 2017 (Medium)** | England | To explore the type of additional exploratory analyses conducted by Evidence Review Groups and their impact on the recommendations made by NICE | A content analysis of relevant documents was undertaken to identify and extract relevant data, and narrative synthesis was used to rationalize and present these data. | 100 most recently completed single technology appraisals since 2009 with published guidance were selected for inclusion | Categories for exploratory analyses developed with research team; this was used to inform coding; all data extraction were double checked by two researchers | The additional analyses undertaken by Evidence Review Groups in the appraisal of company submissions are highly influential in the policy-making and decision- making process; clear influence on 47% of final appraisal determinations | No limitations stated by author(s) |
| **3.3 Cerri et al 2013 (High)** | England | This study examined the impact of evidence, process and context factors on NICE decisions; to assess which of factors best explains the pattern of NICE decisions | With multinomial logistic regression, the relative contribution of explanatory variables on NICE decisions was assessed | A data set of NICE decisions 2004-2009 in HTAs was created, including 32 variables extracted from published information. A three-category decision outcome variable was created | A total of 65 technology appraisals (118 technologies) were analysed | Results showed significant associations ($p<0.10$) between NICE decision outcome and four variables: (i) demonstration of statistical superiority of the primary endpoint in clinical trials by the appraised technology; (ii) the incremental cost-effectiveness ratio (ICER); (iii) the number of pharmaceuticals appraised within the same appraisal; and (iv) the appraisal year. | No limitations stated by author(s) |

| Study | Objective | Country | Study design | Data source | Primary endpoint / Independent variables | Factors that influenced decisions | Limitations |
|---|---|---|---|---|---|---|---|
| 3.4 Clement et al 2009 (High) | To assess how committees use evidence on effectiveness and cost-effectiveness (including any barrier to such use) and what additional factors have influenced decisions | Australia, Canada, England | Descriptive analysis of retrospective data from HTA bodies; 3 case studies: diabetes mellitus, ranibizumab for age-related macular degeneration, and teriparatide for osteoporosis | All publicly available documents as of 31st December 2008 | Primary endpoint used in the supportive clinical studies and categorised end points as clinical endpoints, or surrogate endpoints; for surrogate end points, authors determined whether the committee felt the surrogate was a valid predictor of changes in the relevant clinical end point | Factors that influenced decisions: The differences in listing decisions often appeared less about the interpretation of the clinical or economic evidence and more about differences in agency processes In terms of outcomes: More than 50% of submissions reviewed by NICE used clinical end points (rather than clinical scales or surrogates), and if surrogate outcome were used they were more likely to be judged valid by committee | Use of publicly available sources; there may be subtle issues that were not captured, particularly in the deliberation process; surprisingly few common drugs across the 3 systems, making comparisons across committees less conclusive |
| 3.5 Dakin et al 2014 (Medium) | To investigate the influence of cost-effectiveness and other factors on NICE decisions and whether NICE's decision-making has changed over time | England | Logistic regression to predict whether a technology was recommended or not; NICE's decisions as binary choices for/ against a technology in a specific patient group | Data on all NICE decisions published by December 2011 were obtained from HTAinSite [www.htainsite.com]. | Independent variables comprised of the following: clinical and economic evidence; characteristics of patients, disease or treatment; and contextual factors potentially affecting decision-making. | Cost-effectiveness was main driver for NICE decisions; past decisions appear to have been based on a higher threshold than £20 000–£30 000/QALY; this may reflect consideration of other factors that cannot be easily quantified. | No limitations stated by author(s) |
| 3.6 Drummond & Sorenson 2009 (Medium) | Opinion paper that explains NICE activities, achievements, challenges and lessons learnt | England | Opinion paper | - | - | No direct conclusions; issues discussed around QALY, ICER, sub group analysis and stakeholder involvement | N/A |
| 3.7 Drummond et al 2013 (Medium) | Opinion paper that explores HTA approaches, in both methods and policy, to help bring about reconciliation between | Europe | Opinion paper | - | - | HTA initiatives are likely to give manufacturers an incentive to more closely align their research and development with social objectives; adequate stakeholder involvement is needed to ensure | N/A |

| Study | Aim | Method | Country / Focus | Data sources | Results | Limitations |
|---|---|---|---|---|---|---|
| | different parties and focus on social values and patient perspective | | | | that the values incorporated in HTA processes adequately encompass social values | No limitations stated by author(s) |
| **3.8 Fischer 2012 (High)** | To structure empirical evidence of coverage decisions made in practice based on the components 'methods and evidence', 'criteria and standards', 'decision outcome' and 'processes' | Literature review | Focus on England, scope international | Electronic databases, journals and HTA websites were searched for publications between 1993 and June 2011. Included were analysis of past decisions and application of quantitative methods. | Important influence of therapeutic value where decision makers did not explicitly account for cost-effectiveness; the ICER had significant influence on decisions in Canada, Australia and the UK, but usually in combination with other aspects such as burden of disease or health condition. Budget considerations were significant influences in Australian and Dutch decision-making. | No limitations stated by author(s) |
| **3.9 Kreis and Schmidt 2013 (Low)** | This article explores operational processes and underlying rationales of public engagement at HTA agencies | Authors explored qualitatively public engagement processes and underlying rationales | France, Germany, United Kingdom | The analysis is based on website information, legal framework documents, published and grey literature, and semi structured, in–depth interviews with top officials at these agencies | Engagement processes differed across agencies, particularly regarding the areas in which the public is involved, which groups of the public are involved, what weight they have in influencing decisions, how they are recruited and supported, and how potential conflicts of interests are addressed. | No limitations stated by author(s) |
| **3.10 Nicod and Kanavos 2012 (Medium)** | To identify diverging HTA recommendations across five countries, understand the rationale for decision-making, and suggest ways forward to minimize inter-country difference | Comparative statistical analysis of HTA recommendations for 287 drug-indication pairs appraised by countries between 2007 and 2009, including an in-depth analysis of two case studies | England, Scotland, Sweden, Canada, and Australia | Appraisal reports from each agency. Agreement levels were measured using kappa scores. Associations between the HTA recommendations and the HTA body issuing the recommendation were explored | Substantial disparities in recommendations for/ against drugs; HTA processes potentially influenced by: different priorities in different settings; different perception of benefit and value, and use of different tools of addressing uncertainty; patient preferences and characteristics | No limitations stated by author(s) |

| Study | Aim | Country | Methods | Data collection | Analysis | Findings | Limitations |
|---|---|---|---|---|---|---|---|
| | | | | | through correspondence analysis | seem to weigh more heavily in certain disease areas than other | No limitations stated by author(s) |
| **3.11 Nicod et al 2017 (High)** | To better understand the reasons for differences in reimbursement decisions for orphan drugs in four European countries | England, Scotland, Sweden, France | Semi structured interviews with representatives of HTA bodies | Semi-structured interviews; eight representatives from the four HTA bodies were interviewed between March and June 2015 | An interview topic guide was developed on the basis of findings from a systematic comparison of HTA decisions for 10 orphan drugs. Qualitative thematic data analysis using the framework approach | Decisions regarding orphan drugs made in context of lower quality evidence; threshold of acceptable uncertainty varied by country; NICE more likely to accept surrogate endpoints for orphan drugs; NICE always prefers overall survival to progression-free survival; HRQOL data were considered as a hard end point by NICE. Safety only implicitly considered because already part of marketing authorisation. | |
| **3.12 Oyebode et al 2016 (Low)** | To determine the aspects of expert advice that decision-makers find most useful in the development of evidence-based guidance and to identify the characteristics of experts providing the most useful advice | England | (1) Interviews examined the usefulness of expert advice during guidance development. (2) Associations between usefulness score and characteristics of the expert advisor were investigated using univariate and multivariate analyses | (1) Semi-structured interviews with 17 members of the Interventional Procedures Advisory Committee of NICE. (2) Data were extracted from 211 experts' questionnaires for 41 consecutive procedures. | (1) Transcripts were analysed inductively to identify themes; (2) Usefulness of advice was scored using an index developed through the qualitative work. | Values and challenges of using expert opinion in HTA processes are analysed | Authors reflect on their own potential bias due the researchers' previous experience at NICE and working in public health and medical roles; concept of 'usefulness' was potentially problematic |
| **3.13 Spinner et al 2013 (Medium)** | To assess whether different clinical evidence bases may have influenced listing recommendations | Australia, Canada, England and Wales | Authors reviewed the evidence considered for each listing recommendation, identified the similarities and differences, and evaluated the extent to which different clinical | Appraisal reports between 2007 and 2010 (including manufacturers' submissions) for nine drugs for which the three agencies had | Not provided | Decisions across HTA bodies associated with differences in the clinical evidence base considered. NICE considered indirect and/or mixed-treatment comparisons; in some cases, NICE excluded trials from review if the drug and/or the comparator | Small number of case studies; only publicly available documents were considered |

| Study | Country | Aim | Methods | Data source | Analysis | Results | Limitations |
|---|---|---|---|---|---|---|---|
| *(continued from previous page)* | | | evidence bases could have contributed to different decisions | provided listing recommendations | | were not administered according to the relevant marketing authorization. | |

**Germany (n=14)**

| Study | Country | Aim | Methods | Data source | Analysis | Results | Limitations |
|---|---|---|---|---|---|---|---|
| 3.14 Blome et al 2017 (High) | Germany | To determine methodological requirements for QoL measurement and data presentation in early benefit assessment (EBA) | Qualitative content analysis based on documents of all EBAs completed by 2014; analysis included information extraction, coding, critical discussion an consensus building | Documents publicly available on the G-BA website including: manufacturer dossier; dossier evaluation and benefit assessment by IQWiG or Federal Joint Committee (G-BA); protocol of the oral hearing; rationale of the G-BA decision ("Tragende Gruende"=main justifications) | Documents were searched for the term QoL; Relevant passages of all EBAs of 2011–2013 were independently extracted and reduced to key content by two researchers. Recurring patterns were identified and verified through comparison with EBAs of 2014. | No association between the inclusion of QoL data in benefit dossiers and the G-BA's rating decision might be explained by non-compliance with the various methodological requirements found in our analysis, so that in most cases, the mere inclusion of QoL data in the dossier did not lead to a positive evaluation of QoL benefit. In addition, many EBAs did include QoL outcomes, but there were no statistically or clinically significant effects | No limitations stated by author(s) |
| 3.15 Fischer and Stargardt 2014 (Medium) | Germany | To explain the decisions made in early benefit assessments (EBAs), clarify the roles of manufacturers, IQWiG, German Federal Joint Committee (G-BA), and guide manufacturers in developing future submissions | Authors evaluated differences in rating decisions by manufacturers, the IQWiG, and the G-BA with regard to each pharmaceutical's added benefit. Authors used Cohen's kappa to analyze agreement between rating decisions; chi-square test and bivariate regression were used to identify associations between components of the EBA | Data extracted for EBAs for which the G-BA made a rating decision between 2011 and 2013. Authors developed a variable list including: rating decisions of manufacturers, IQWiG, G-BA; characteristics of the process; types of evidence submitted; methods used to | Two independent reviewers extracted data. Once completed, the worksheets were compared to identify any deviations. Interrater reliability was good, with an average Cohen's kappa coefficient of 0.63 (range, 0.28 to 1.00) for categorical variables and an average Pearson's correlation coefficient of 0.80 | While the G-BA tended to disagree with the rating of benefit by manufacturers, it softened IQWiG's decisions, potentially to make the final outcome more acceptable. Concerns voiced that the G-BA might be exceeding its statutory authority by taking cost or procedural considerations into account appear to be unfounded. Choosing appropriate evidence to submit for each endpoint remained a challenge, as submission of | No limitations stated by author(s) |

| Study | Objective | Focus/Country | Methods | Data source | Results | Limitations |
|---|---|---|---|---|---|---|
| | | | process and the rating decisions of the G-BA | generate evidence; and pharmaceutical's maximum possible budget impact. | for continuous variables (range, –0.18 to 1.00). Any disagreement was resolved through discussion between the authors. | health outcomes evidently influenced decisions. |
| **3.16 Fischer et al 2016 (Medium)** | To analyse whether decisions of the German regulatory agency (G-BA) deviate from decisions from HTA or regulatory agencies in England (NICE), Scotland (SMC) and Australia (PBAC). | Focus on Germany, compared with England, Scotland, Australia | Authors analysed statistically decisions made for comparable patient subgroups by the four agencies between 2011 and 2014. First, decisions were compared (a) by their final outcome, i.e. whether a health benefit was identified, and (b) by the agencies' judgement on comparative effectiveness. Subsequently, they partially explored reasons for differences between HTA agencies. | All early benefit assessments of G-BA completed between January 2011 and December 2014; for G-BA decisions and information on the corresponding EBAs, the database developed by the Hamburg Center for Health Economics (HCHE) was used; otherwise documents available from HTA websites | For each comparison, authors analysed the agreement between G-BA and each of the other HTA agencies. Agreement was quantified by calculating Cohen's Kappa, to determine whether agreement between two raters was by chance | G-BA deviated considerably in decisions compared to other HTA agencies; G-BA tends to appraise stricter than NICE.

HTA Agencies differed in accepting endpoints such as recognising the surrogate endpoint progression-free-survival. Another example is to prefer disease-specific mortality over over-all mortality as endpoint or vice versa. Other factors in which agencies were different: choice of comparator(s); differences in handling lack of evidence

Agreement in endpoints between the agencies was highest for adverse events and quality of life followed by mortality; for morbidity, G-BA and the other agencies agreed least often | No limitations stated by author(s) |
| **3.17 Ivandic et al 2014 (High)** | To explore to which extent methodological requirements of HTA agencies differ between Germany and England | Germany, England | The following aspects were examined: guidance texts on methodology and information sources for the assessment; clinical study design and methodology; statistical analysis, quality of evidence base, extrapolation of results (modelling), and generalisability of study | Not stated; publicly available information on methods from legal and guidance documents from HTA websites | The findings are presented separately for the two HTA systems and thus may serve as stand-alone references. A concise, integrated comparison follows to highlight the main similarities and | Methodological requirements differed mainly in the acceptance of low-level evidence, surrogate endpoints, and data modeling. Some of the discrepancies may be explained, at least in part, by differences in the health care system and procedural aspects (e.g. timing of assessment). | No limitations stated by author(s) |

| Study | Country | Objective | Methods | Data source | Methodological requirements | Results | Limitations |
|---|---|---|---|---|---|---|---|
| | | | results; and categorisation of outcome | | differences in the methodological requirements. | | |
| **3.18 Griffith and Griffith 2015 (Low)** | Germany | Analysis of past decisions of German HTA to inform future submissions | All IQWiG decisions from January 2011 to May 2015 were assessed, and the effect of the clinical evidence base on the submission outcome was examined. | Completed single drug appraisals from Jan 2011 to May 2015 | Recommendation ('added benefit' or 'no added benefit'), indication, rationale, and evidence base were extracted | Over half of drugs appraised by IQWiG since 2011 have been given 'no added benefit' status, and direct evidence against an appropriate comparator remains a priority for a favourable decision | No limitations stated by author(s) |
| **3.19 Kohler et al 2015 (Medium)** | Germany | To determine the information gain from AMNOG documents compared with non-AMNOG documents for methods and results of studies available at market entry of new drugs. | Authors assessed reporting quality for each study and each available document for eight methods and 11 results items For each document type they calculated the proportion of items with complete reporting for methods and results, for each item and overall, and compared the findings. | Dossier assessments conducted by IQWiG between 1 Jan 2011 and 28 Feb 2013; European public assessment reports, journal publications, and registry reports. | Not provided | Concludes that AMNOG documents provide a considerably higher proportion of complete information than European public assessment reports; this includes information on methods, results and patient relevant outcomes. The information gap was most striking when the drug was approved only in a certain subpopulation. | Small sample |
| **3.20 Kvitkina et al 2014 (Low)** | Germany | To describe the feasibility of the early benefit assessment on the basis of patient-relevant outcomes by systematically characterising the outcomes available in manufacturers' dossiers and comparing the companies' and IQWiG's evaluations regarding patient relevance and surrogate validity | Dossier assessments were used for data extraction; the outcomes available and the respective evaluations were extracted and compared. 12 out of 22 submitted dossiers contained sufficient data to assess outcomes; all 12 assessable dossiers provided data on patient-relevant outcomes. | Publicly available manufacturers' dossiers; published between October 2011 and June 2012 | Not provided | Data on mortality and adverse events were available in almost all dossiers; data on morbidity and health-related quality of life available in 8 and 7 dossiers, respectively. Of a total of 214 outcomes extracted by IQWiG, 124 patient-relevant and 3 surrogate outcomes were included in IQWiG's assessment (companies: a total of 183 outcomes included, of which 172 were patient-relevant and 11 were surrogates outcomes partly deviated from each other. | No limitations stated by author(s) |

| Study | Aim | Country | Methods | Data | Findings | Limitations |
|---|---|---|---|---|---|---|
| **3.21 Lauenroth and Stargardt 2017 (High)** | To analyze how value is determined within the scope of the German Pharmaceutical Restructuring Act | Germany | Generalized linear model regression to analyze impact of added benefit on difference between negotiated prices and prices of comparators | All pharmaceuticals that had undergone assessment, appraisal, and price negotiations in Germany before June 30, 2016 | Data were extracted from G-BA databases; added benefit was defined in various ways; in all models, they controlled for additional criteria such as size of patient population, European price levels, and whether the comparators were generic. | Authors conclude that price premiums were driven by health gain, the proportion of people benefitting from a pharmaceutical, European price levels, and whether the comparator was generic. QoL did not play a role in current decision making | No limitations stated by author(s) |
| **3.22 Leverkus and Chuang-Stein 2016 (Medium)** | To investigate requirements of benefit assessment with special attention on: choice of the comparator, patient relevant endpoints, subgroup analyses, extent of benefit, determination of net benefit, primary and secondary endpoints, and uncertainty of the additional benefit. | Germany | Authors state they contrast the approaches taken by the G-BA and IQWiG with those of the European Medicines Agency (EMA). | Authors referenced IQWiG's General Methods paper, German Social Code Book, and G-BA's Rules of Procedure. | For principles underlying regulatory decisions, they reference primarily the International Conference on Harmonization (ICH) E9 (Statistical Principles for ClinicalTrials, 1998) document. | Provides comprehensive overview and opinion on methodological requirements and issues in German HTA process, with particular focus on the role of outcomes and evidence types | No limitations stated by author(s) |
| **3.23 Lohrberg et al 2016 (High)** | To analyse how QoL is defined in early benefit assessment (EBA) and which role does it play | Germany | Qualitative analysis all benefit assessments completed by the end of 2013 were processed. Additionally, data on the decision outcomes were collected and analysed | Publicly available dossiers (summaries), dossier evaluations, protocols of the oral hearings, the final resolutions of the Federal Joint Committee (G-BA) and main | Documents were imported to software and searched for QoL terms; resulting paragraphs were reduced and summarized by two researchers; coding was performed on the basis of summaries | QoL has not been well defined in HTA processes and does not inform final decisions; they identified the absence or the inappropriate presentation of QoL data; at the same time stakeholders saw the value and importance of including QoL in EBA | No limitations stated by author(s) |

| Study | Objective | Country | Methods | Data source | Analysis | Findings | Limitations |
|---|---|---|---|---|---|---|---|
| | | | | justifications completed by 2013 (n = 66) | | | |
| **3.24 Riedel et al 2014 (Low)** | To explain some fundamental concepts in Health Economic Evaluations (HEE) and how these concepts are adapted in different countries, notably in Germany | Germany focused, international | Bibliographic search to identify existing methods of health economic evaluation of new drugs used by HTA agencies in 11 countries and comparison with German HTA agency | Published literature | - | Although the core principles of HEE are very similar worldwide, there is a lack of harmonization. Overcoming the fourth hurdle (the reimbursement hurdle) is likely to be increasingly challenging for new drugs. | No limitations stated by author(s) |
| **3.25 Ruof et al 2014 (a) (High)** | To analyse the outcomes 18 months after introduction of the new AMNOG legislation on early benefits assessments (EBA) | Germany | All EBAs commenced prior to June 2012 were included and analysed (proportions were calculated; no statistical analysis was carried out) | The G-BA website (http://www.g-ba.de/informationen/nutzenbewertung) was used to obtain manufacturers' benefit dossiers, IQWiG assessments, and G-BA decisions | 27 EBAs were analysed in regards to: additional benefit, appropriate comparative therapy (ACT), patient-relevant endpoints, and adverse events | Considerable variance was observed in additional benefit reported by manufacturers, IQWiG and G-BA. Areas of disagreement included comparator selection, definition of subgroups and patient-relevant endpoints, and classification and balancing of adverse events. | No limitations stated by author(s) |
| **3.26 Ruof et al 2014 (b) (High)** | To compare endpoints and related benefit categories used in marketing authorisation to those considered by G-BA in the field of oncology | Germany | Evaluation of early benefit assessments (EBAs) in oncology commencing prior to 31 December 2013 | The Summary of Product Characteristics (SPC) for the respective marketing authorisations was derived from the website of the EMA. | Clinical trial endpoints that supported the marketing authorisation and the benefit assessment were derived from (i) the SPCs, (ii) manufacturers' value dossiers and (iii) the G-BA value decisions | Inconsistencies in acceptance of morbidity and QoL outcomes between G-BA and EMA; EMA accepted well established and clinically relevant morbidity endpoints (e.g. progression-free survival and response rate), which were mostly excluded by G-BA; final decisions by G-BA mostly driven by mortality outcomes | No limitations stated by author(s) |
| **3.27 Staab et al 2016 (High)** | To evaluate the acceptance of clinically | Germany | Medicines for oncological, metabolic and infectious diseases with EBAs | Manufacturer's dossiers, regulatory | Documents were analysed to determine patient | Inconsistencies were identified in patient relevance of morbidity-related PEPs as well as in | No limitations stated by author(s) |

| Study | Aim | Country | Methods | Data sources | Results | Findings | Limitations |
|---|---|---|---|---|---|---|---|
| | technologies for use in the Netherlands | | Kruskal-Wallis for not normally distributed indicators. A multinomial logit regression was used in the analysis to model the probabilities associated with the three types of technology appraisal outcome. | extracted from published information. | 2 were considered restricted; | associated with introduction of the technology, (3) therapeutic indication and (4) prevalence of the target population. Results confirm the value of a comprehensive and multivariate approach to understanding CVZ decision-making. | |
| 3.30 Franken et al 2013 (Medium) | To investigate the role of pharmacoeconomic evidence in drug reimbursement decision making; and (ii) to determine the extent to which appraising the importance of full economic evaluations relative to other evidence is a transparent process | Netherlands, Sweden | Authors investigated all reimbursement dossiers published in the period January 2005 to July 2011. | Data sources included all Dutch and Swedish drug reimbursement information published in the period January 2005 to July 2011 | The analysis started in 2005 because that was the first year in which pharmacoeconomic evidence was required for reimbursement decision making in The Netherlands. | Therapeutic value appeared to be the most decisive criterion; the relative importance of full economic evaluations is more modest than would generally be expected, especially in The Netherlands; both countries could make the appraisal process more transparent by more explicitly showing the role of different criteria. | Reliance on publicly available data sources |
| 3.31 Le Polain et al 2010 (Medium) | To describe and critically evaluate drug reimbursement decision processes, to identify their strengths and weaknesses and to formulate general policy recommendations. | Austria, Belgium, France, the Netherlands and Sweden | Comparative study (1) for the description of drug reimbursement decision processes, authors used the Hutton framework; (2) systems were evaluated using accountability for reasonableness framework by Daniels and Sabin. | Literature, policy documents and interviews with stakeholders | - | The paper provides a wide range of information on assessment and appraisal processes of Dutch HTA, and draws conclusions about criteria: For example, although there is no formal hierarchy in assessment criteria, most interviewees stated that effectiveness, efficacy and side effects were often the most important criteria determining the therapeutic value. Interviewees also acknowledged that the majority of time in a meeting of the Dutch HTA is devoted to determining the therapeutic value, less time is spent on | Analysis took place in supply-driven context; it was beyond the scope of this study to explore opportunities to move towards demand-driven system, where the societal needs drive the industry's strategic plan |

| Study | Aim | Country | Study type | | Summary | |
|---|---|---|---|---|---|---|
| | | | | | assessing cost-effectiveness evidence. | N/A |
| **3.32 Stolk et al 2009 (Medium)** | To review the current approach to HTA used in The Netherlands in medical specialist care; the authors seek to provide a basic understanding of the strengths and weaknesses of the specific practices and processes | Netherlands | Opinion paper | - | Authors explore trends in future of (Dutch) HTA: What can be expected is a growing incentive for all parties to generate HTA data; increasing trend for conditional reimbursement linked to requirements for data collection and further study; further work is needed to understand how assessments and procedures jointly affect decision-making and to develop best practice guidelines; broader appraisals might be needed where the assessment will also cover optimal positioning of a service amongst the variety of services available to patients | N/A |
| **3.33 Versteegh et al 2016 (Medium)** | In this editorial, the authors highlight the distinguishing features of the new Dutch guidelines for economic evaluation; and highlight which developments, in their opinion, are desirable in coming updates, but are still in development or controversial | Netherlands | Editorial | - | New guidelines set preference for QALYs measured with the EQ-5D if appropriate but also offer alternative approaches for areas in which QoL might not be appropriate such as: prevention; diagnostics; medical devices; long-term care; forensics; reference is also made to multi-criteria decision making | N/A |

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# Supplement 4: HTA documents analysed for case studies

## National Institute for Health and care Excellence (NICE), England

**Draft documents for consultation**

**4.1 Health Technology Appraisal Donepezil, galantamine, rivastigmine and memantine for the treatment of mild to moderate Alzheimer's disease (Part review of TA 111) Draft scope**

**4.2 Alzheimer's disease - donepezil, galantamine, rivastigmine and memantine (review): appraisal consultation document (online)**

**Final documents**

**4.3 Health Technology Appraisal Donepezil, galantamine, rivastigmine and memantine for the treatment of Alzheimer's disease (Review of TA 111) Final Scope**

**4.4 Final Appraisal Determination Donepezil, galantamine, rivastigmine and memantine for the treatment of Alzheimer's disease (review of NICE technology appraisal guidance 111)**

**Reports by the Assessment group**

**4.5 The effectiveness and cost-effectiveness of donepezil, galantamine, rivastigmine and memantine for the treatment of Alzheimer's disease (review of TA111): a systematic review and economic model, Produced by: Peninsula Technology Assessment Group (PenTAG), University of Exeter [Note that this includes a revised section on results]**

**4.6 Overview Donepezil, galantamine, rivastigmine and memantine for the treatment of Alzheimer's disease   (Review of NICE technology appraisal guidance 111)**

**Comments to Technology Assessment Report (TAR)**

**4.7 Donepezil, galantamine, rivastigmine and memantine for the treatment of Alzheimer's disease (Review of TA 111), Responses by various stakeholders including: Eisai/Pfizer; NHS Quality Improvement Scotland; NHS West Kent and NHS Islington;  Novartis; Shire Pharmaceuticals; Alzheimer's Society; RICE (The Research Institute for the Care of Older People); Lundbeck**

**Responses by Assessment Group**

**4.8 NICE Health Technology Appraisal, Donepezil, galantamine, rivastigmine and memantine for the treatment of Alzheimer's disease (review of TA 111), Response to consultee and commentator comments on the draft remit and draft scope**

**4.9 NICE, Health Technology Appraisal, Donepezil, galantamine, rivastigmine and memantine for the treatment of Alzheimer's disease (review of NICE technology appraisal guidance 111)   Response to consultee, commentator and public comments on the Appraisal Consultation Document (ACD)**

**4.10 AChEIs and memantine for Alzheimer's Disease, PenTAG responses to Consultee comments 17th August 2010**

**Submissions**

**4.11 Various submissions including by manufacturers and other stakeholders e.g. Alzheimer's Society Report; British Geriatrics Society; Royal College of Psychiatrists (Faculty of old age psychiatry); NHS Quality Improvement Scotland**


## Institut für Qualität und Wirtschaflichkeit im Gesundheitswesen (IQWiG), Germany

**Cholinesterase Inhibitors: Donezepil, Galantamin, Rivastigmin**

**4.12 Berichtsplan zum Bericht „Cholinesterasehemmer bei Alzheimer Demenz" , [Auftrag A05-19A], Version 1.0 Stand: 02. Juni 2005; Report plan. Last accessed 10th January 2018**

**4.13 Amendment 1 zum Berichtsplan „Cholinesterasehemmer bei Alzheimer Demenz", [Auftrag A05/19A] , 12.06.2006; Amendment 1 to Report Plan version 1.0. Last accessed 10th January 2018**

**4.14 IQWiG. Cholinesterasehemmer bei Alzheimer Demenz. Vorbericht A05/19-A. Köln: Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (IQWiG); September 2006. [Preliminary report] Last accessed 10th January 2018**

**4.15 IQWiG: Cholinesterase inhibitors in Alzheimer's disease. Final report A05-19A. Cologne: Institute for Quality and Efficiency in Health Care (IQWiG); February 2007. Last accessed 10th January 2018**

**4.16 IQWiG. Cholinesterasehemmer bei Alzheimer Demenz. Abschlussbericht A05-19A. Köln: Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (IQWiG); Februar 2007. Last accessed 10th January 2018** [→ this is the German version of 4.15; in addition to 4.15 it includes the documented stakeholder involvement through meeting and written consultation]

**Memantine**

**4.17** Berichtsplan zum Bericht „Memantin bei Alzheimer Demenz" [Auftrag A05-19C] Version 1.0 Stand: 24. August 2005, Report plan version1. Last accessed 10th January 2018

**4.18** Amendment 1 zum Berichtsplan „Memantin bei Alzheimer Demenz" [Auftrag A05/19C], 12.06.2006; Amendment 1 to the report plan version. Last accessed 10th January 2018

**4.19** Amendment 2 zum Berichtsplan Memantin bei Alzheimer Demenz, Auftrag A05-19C Version 1.0 Stand: 06.08.2007; Amendment 2 to the report plan version. Last accessed 10th January 2018

**4.20** Memantin bei Alzheimer Demenz, Dokumentation and Würdigung der Stellungnahmen zum Berichtsplan, Auftrag A05-19C Version 1.0 Stand: 11.02.2008 ; documentation and appraisal of comments on the report plan version 1.0. Last accessed 10th January 2018

**4.21** Memantin bei Alzheimer Demenz, Berichtsplan, Auftrag A05-19C Version 2.0 Stand: 11.02.2008 ; Report plan version 2.0. Last accessed 10th January 2018

**4.22** Memantin bei Alzheimer Demenz Vorbericht (vorläufige Nutzenbewertung), Auftrag A05-19C Version 1.0 Stand: 01.08.2008 ; Preliminary report. Last accessed 10th January 2018

**4.23** Memantin bei Alzheimer Demenz, Dokumentation und Würdigung der Stellungnahmen zum Vorbericht, Auftrag A05-19C Version 1.0 Stand: 28.04.2009.; Documentation and appraisal of comments on the preliminary report. Last accessed 10th January 2018

**4.24** IQWiG-Berichte – Jahr: 2009 Nr. 59 Memantin bei Alzheimer Demenz, Abschlussbericht, Auftrag A05-19C Version 1.0 Stand: 08.07.2009 Final report. Last accessed 10th January 2018

**4.25** Tragende Gründe zum Beschluss des Gemeinsamen Bundesausschusses über die Einleitung eines Stellungnahmeverfahrens zur Änderung der Arzneimittel-Richtlinie (AM-RL): Anlage III – Übersicht der Verordnungseinschränkungen und –ausschlüsse Memantin, Vom 10. August 2010. Last accessed 10th January 2018


## Zorginstituut Nederland, previously: College voor Zorgverzekeringen (CVZ), Netherlands

**4.26** CFH rapport 07/11 memantine (Ebixa®), (2e)herbeoordeling, Op 2 april 2007 uitgebracht aan de minister van Volksgezondheid, Welzijn en Sport

**4.27** GVS-rapport 13/11 donepezil (hydrochloride) Aspen® Vastgesteld op 24 juni 2013, College voor zorgverzekeringen, Diemen.

**4.28** Farmacotherapeutisch rapport rivastigmine (Exelon®) bij Parkinsondementie, 2006

# Supplement 5: List of stakeholders involved in HTAs as identified in case studies

| ENGLAND | |
|---|---|
| **Stakeholder group: Manufacturers** | |
| Accord Healthcare (donepezil) | Novartis (rivastigmine) |
| Aspire Pharma (galantamine, rivastigmine) | Pfizer (donepezil) |
| Actavis UK (all four drugs) | Ranbaxy (donepezil) |
| Consilient Healthcare (galantamine, memantine) | Sandoz (all four drugs) |
| Dr Reddy's Laboratories (all but galatamine) | Shire (galantamine) |
| Eisai (donepezil) | Teva UK (all four drugs) |
| Lundbeck Ltd (memantine) | Wockhard UK (donezepil) |
| Mylan (galantamine, memantine) | Zentiva UK (all but rivastigmine) |
| **Stakeholder group: Patient/ carer groups** | |

| | |
|---|---|
| Afiya trust | Mental Health Foundation |
| Alzheimer's Society | Muslim Council of Britain |
| Carers UK | Muslim Health Network |
| Disability Rights UK | Neurological Alliance |
| Equalities National Council | Neurosupport |
| Innovations in Dementia | South Asian Health Foundation |
| Leonard Cheshire Disability | Specialised Healthcare Alliance |

**Stakeholder group: Professional associations**

| | |
|---|---|
| Association of British Neurologists | Royal College of General Practitioners |
| Association of Directors of Adult Social Services | Royal College of Nursing |
| British Geriatrics Society | Royal College of Pathologists |
| British Neuropathological Society | Royal College of Physicians |
| British Neuropsychiatry Association | Royal College of Psychiatrists |
| College of mental health Pharmacy | Royal Pharmaceutical Society |
| Dementia Action Alliance | Royal Society of Medicine |
| Institute of Neurology | United Kingdom Clinical Pharmacy Association |
| Primary Care Neurology Society | |

Others

| | |
|---|---|
| Department of Health | NHS South Eastern Hampshire CCG |
| NHS England | Welsh Government |
| NHS Somerset CCG | |

**GERMANY**

| **Stakeholder** | **English translation or description** |
|---|---|
| **Technology Assessment for Memantine** | |
| Bundesverband für Gesundheitsinformation und Verbraucherschutz e. V. | Association for health information for the public and consumer protection (charity) |
| Deutsche Alzheimer Gesellschaft e.V | German charity for Alzheimer |
| Deutsche Gesellschaft für Neurologie; Deutsche Gesellschaft für Psychiatrie, Psychotherapie und Nervenheilkunde | Professional association for psychiatry, psychotherapy and neurology |
| Hirnliga e.V. | Charity for the brain; refers to Alzheimer |
| Institut für angewandte Statistik | Institute for applied statistics |
| Institut für Arzneimittelsicherheit in der Psychiatrie | Institute for safety of psychiatric drugs |
| Karolinska Institutet | Swedish medical university |
| Kompetenznetz Demenz | Network for researchers, clinicians, people living with Alzheimer and their families |
| Lundbeck GmbH | Pharma company |
| Merz Pharmaceuticals GmbH | Pharma company |
| Novartis Pharma GmbH | Pharma company |
| The Research Institute for the Care of Older People (RICE) | / |
| Verband Forschender Arzneimittelhersteller e. V. (VFA) | Association of pharma companies involved in research |

| | |
|---|---|
| Verein zur Förderung der Forschung auf dem Gebiet der experimentellen Neurologie | Association to promote research in neurology |
| **Technology Assessment for Cholinesterase inhibitors** ||
| Eisai GmbH | Pharma |
| Novartis GmbH | Pharma |
| Pfizer GmbH | Pharma |
| Janssen-Cilag GmbH | Pharma |
| Merz Pharmaceuticals GmbH | Pharma |
| Verband Forschender Arzneimittelhersteller e.V. | Association of Pharma Companies involved in Research |
| University of Manchester | University, England (UK) |
| Alzheimer-Ethik e.V. | Charity for Alzheimer, founded by carers |
| Universitätsklinikum Freiburg | University |
| Deutsche Gesellschaft für Gerontologie und Geriatrie | German Society of Gerontology and Geriatrics |
| Arznei-Telegramm | News magazine about drugs |
| Deutsche Gesellschaft f. Gerontopsychiatrie und –psychotherapie (DGGPP) e. V. | German Psychogeriatric Association |
| Deutsche Alzheimer Gesellschaft e. V. | German Alzheimer Association (charity) |
| Universitätsklinikum Hamburg-Eppendorf | Medical University in Hamburg, Germany |
| Kompetenznetz Demenzen | Network for dementia |
| Hirnliga e.V. | Charity for the Brain, specifically Dementia |
| Bezirkskrankenhaus Günzburg | Hospital |
| Institut für Klinische Pharmakologie, Klinikum Bremen-Mitte | Pharmacological Institute, Medical university |