EEPRU

Economic Evaluation of Health and Social Care Interventions Policy Research Unit

RESEARCH REPORT

# Whole pathway modelling of depression in patients with diabetes (Theme 2: Mental Health)
# Part 2: Independent economic evaluation: methods and results, discussion and conclusion

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The Department of Health's Policy Research Unit in Economic Evaluation of Health and Care Interventions is a 5 year programme of work that started in January 2011. The unit is led by Professor John Brazier (Director, University of Sheffield) and Professor Mark Sculpher (Deputy Director, University of York) with the aim of assisting policy makers in the Department of Health to improve the allocation of resources in health and social care.

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This is the second part in the EEPRU report 'Whole pathway modelling of depression in patients with diabetes'. The first part contains an introduction to the project and decision problem, details on the review of the literature (including the existing health economic literature), and conceptual modelling. The executive summary is found in both parts. Numberings of chapters, figures and tables all carry-on from those in part 1. The executive summary is found in both parts. All appendices are available in a separate file. All files may be found on the EEPRU website (http://www.eepru.org.uk/).

**Abbreviations**

| | |
|---|---|
| ACCORD | Action to Control Cardiovascular Risk in Diabetes |
| BDI | Becks Depression Inventory |
| BNF | British National Formulary |
| CAD | Coronary artery disease |
| CBT | Cognitive behavioural therapy |
| CES-D | Center of Epidemiological Studies - Depression |
| CG | Clinical guideline |
| CHD | Coronary heart disease |
| CHF | Congestive heart failure |
| CI | Confidence interval |
| CIDI | Composite International Diagnostic Interview |
| CMHT | Community Mental Health Teams |
| DES | Discrete event simulation |
| DESM | Discrete event simulation model |
| DESMOND | Diabetes Education and Self-Management for Ongoing and Newly Diagnosed |
| DM/D | Diabetes and depression |
| DoH | Department of Health |
| DSM | Diagnostic and Statistical Manual of Mental Disorders |
| EEPRU | Economic Evaluation Policy Research Unit |
| GP | General practitioner |
| HADS | Hospital Anxiety and Depression Scale |
| HR | Hazard ratio |
| HRQoL | Health-related quality of life |
| IAPT | Improving Access to Psychological Therapies |
| ICD | International Classification of Diseases |
| ICER | Incremental cost-effectiveness ratio |
| IHD | Ischaemic heart disease |
| LTC | Long-term condition |
| LY | Life year |
| MD | Mean difference |
| MI | Myocardial infarction |
| NDA | National Diabetes Audit |

| | |
|---|---|
| NHS | National Health Service |
| NICE | National Institute for Health and Care Excellence |
| OM | Outcomes model |
| OR | Odds ratio |
| PAID | Problem Areas In Diabetes |
| PHQ | Patient Health Questionnaire |
| PSA | Probabilistic sensitivity analysis |
| PSSRU | Personal Social Services Research Unit |
| PTM | Post-trial monitoring |
| QALY | Quality-adjusted life year |
| QOF | Quality and Outcomes Framework |
| QoL | Quality of life |
| RCT | Randomised controlled trial |
| RR | Relative risk (also known as risk ratio) |
| SPS | Specialist Psychotherapy Services |
| T1DM | Type 1 diabetes mellitus |
| T2DM | Type 2 diabetes mellitus |
| TAU | Treatment as usual |
| UK | United Kingdom |
| UKPDS | United Kingdom Prospective Diabetes Study |
| USA | United States of America |

## Executive Summary

### Background

Diabetes is associated with premature death, along with a number of serious complications such as amputation, blindness and heart disease. The presence of diabetes with comorbid depression increases both the risk of mortality and the prevalence of complications, as well as resulting in increased healthcare use and costs.

Historically care pathways for diabetes and for depression have been isolated from each other, resulting in a siloing of care. There is now interest in exploring methods by which the care pathways may be integrated, and the impact that this has on both patient outcomes and costs to the healthcare system.

### Objectives

This project aimed to assess the health economic outcomes associated with having both diabetes and depression, and explore potential changes to the care pathways for these diseases that could be implemented to improve the health economic outcomes.

### Data Sources

Data were drawn from a range of sources including published literature identified through a series of searches. A scoping review in MEDLINE identified pooled data, followed by subsequent searches in MEDLINE, PsychInfo and Cochrane electronic databases for individual studies where no pooled data was available. Searches were conducted from July to November 2013. These searches were supplemented by papers identified through consultation with experts and by papers known to the authors.

### Methods

The objective of the literature review was to understand the relationship between diabetes and depression to inform the model development and to identify evidence that may be used to populate the economic model. The search aimed to identify information for multiple parameters. The review of the literature consisted of 3 steps. Firstly, a scoping review of reviews was conducted to inform the model conceptualisation. This aimed to identify all types of reviews (narrative, systematic and meta-analytic) relating to depression in diabetes. Secondly, after the model had been developed, targeted searches were conducted to identify studies for parameters where suitable data had not

been identified in the reviews. Finally, a systematic search was conducted to provide a more comprehensive understanding of a "key" model parameter, namely the relationship between diabetes-related complications and depression.

A mathematical model of the depression care pathways experienced by people with diagnosed type-2 diabetes (T2DM) in England was created based on the conceptual model developed with the aid of an advisory group supplemented by a review of the published literature and a meeting with current service users. This model took the form of a discrete-event simulation, and was developed to assess the relative cost-effectiveness of proposed service changes from an NHS perspective, wider social benefits were also explored. The population considered for this project was adults with T2DM currently managed within primary care in England. Patients could have existing depression, develop depression, or remain depression free.

The health economic outcomes considered were morbidity, quality of life, mortality, and costs incurred by the healthcare system. The potential service changes (interventions) considered included: improvements in opportunistic screening for depression; collaborative care; both improvements in opportunistic screening for depression and collaborative care. The comparator was current standard care. An expert group of advisors assisted in the identification of relevant service changes and identification of relevant evidence.

**Results**

Sixty reviews of depression in diabetes were identified in the scoping search. Insufficient data was identified in the reviews to populate all of the model parameters. Targeted searches were therefore conducted to identify data from individual studies for: the prevalence of depression amongst T2DM in England; the natural history of depression in diabetes, including incidence, recurrence, relapse and persistence; and the effectiveness of screening for depression in diabetes. A review was also conducted to identify evidence on the link between the development of diabetes-related complications and depression, and the converse.

The model estimated that the proposed policies have the potential to reduce both the time spent with depression, and the number of diabetes-related complications experienced. All three policies were associated with an improvement in quality of life and an increase in depression-free years compared with current practice, but with an increase in health care costs. Overall Policy 3, which examined the effect of introducing both collaborative care and increasing opportunistic screening

together, was estimated to produce the greatest benefits in terms of both events avoided and depression free years. However, the incremental cost-effectiveness ratio (£37,421) comparing Policy 3 to current practice is above the cost per QALY currently considered cost-effective. In addition, when comparing across the policies, Policy 2 (improvement in opportunistic screening) is dominated by Policy 1 (collaborative care), and comparing Policy 3 with Policy 1, this policy would again not be considered cost-effective (with an ICER of £68,017) when assuming a willingness to pay threshold of either £20,000 or £30,000 per QALY. However, these estimates do not take into account the uncertainty surrounding both parameters and structural assumptions. All three policies produced some benefits when looking at a wider societal perspective and were associated with a reduction in both the number of days off sick due to ill health and the need for informal care.

Additional research is required to decrease the uncertainty in the results presented, such as in the bi-directional relationship between diabetes and depression, and the natural history of depression in patients with diabetes.

While this study examined the effects of policies in patients with diabetes, the proposed changes to the pathway are potentially generalizable to patients with other long term physical conditions predominantly treated within primary care.

Using the evidence currently available, the results of this research suggest that policies targeted at identifying and treating depression early in patients with diabetes may lead to a reduction in diabetes related complications and depression, which in turn increase life expectancy and health related quality of life. Although there is an increase in overall health care costs, the results show that this is below the willingness to pay threshold currently considered acceptable in England.

## 5 Independent economic evaluation

This project focuses on changes to the depression services of care (including screening for depression and management of depression) for patients with diabetes. Changes to the diabetes services of care are not considered as this was outside the scope of the project.

Informed by the final agreed conceptual model, a mathematical economic model was constructed using Simul8 software. As is normal in health care modelling, the mathematical model represents a simplification of the reality [1] but includes all the elements considered essential (identified at the conceptual stage) by the advisory group and service users when evidence was available.

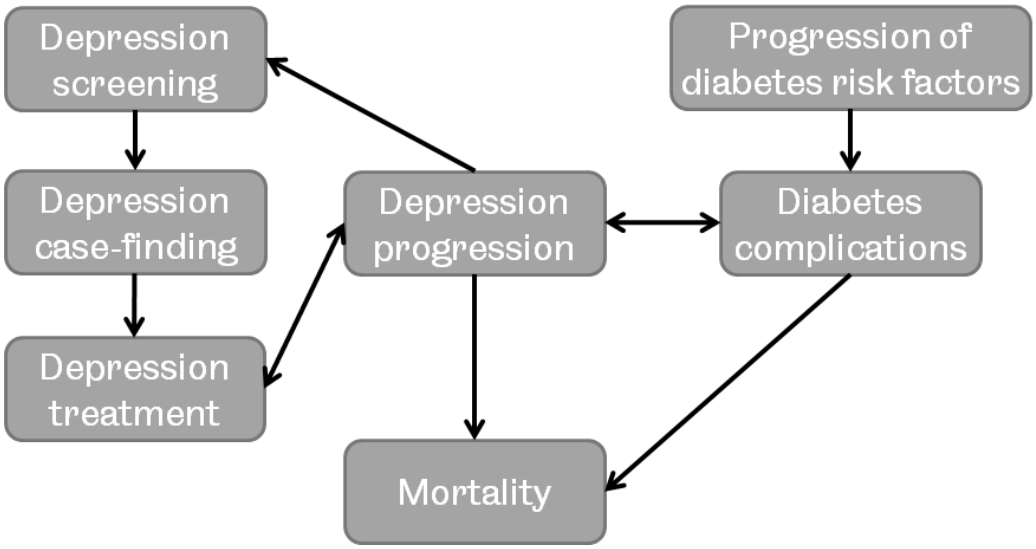
Due to the number and diverse nature of parameters required for the economic model, it was not possible to perform exhaustive and systematic searches for each parameter. Consequently, parameters were taken from evidence identified during scoping searches when possible, supplemented by evidence identified from a series of targeted searches (non-exhaustive or systematic) when appropriate (section 2). Assumptions were used when no evidence was identified.

### 5.1 Overview of the model structure

In summary, the economic model consists of inter-locking disease-specific models (Figure 9):

- The diabetes sub-model captures the development of diabetes-related complications (micro and macrovascular) over time.
- The depression sub-model captures the natural history of the progression of depression and the care pathway in England in terms of screening, case-finding and management of depression.
- The bi-directional relationship between depression and diabetes is modelled through diabetes-related complications. In the economic model, individuals with diabetes-related complications are more likely to experience depression; whilst patients with depression are more likely to develop diabetes-related complications.

**Figure 9: Simplified schematic of the economic model**




The economic model considers a cohort of patients (with different baseline characteristics) representative of the diagnosed T2DM population in England. Patients who enter the model can either have current depression (either on treatment or untreated), have a history of depression (but not currently depressed and therefore not on treatment) or never been depressed (no history or current depression). Each patient is followed over time, with the progression of diabetes-related risk factors (such as HbA1c, blood pressure, BMI) modelled using evidence available to estimate the risk of developing micro and/or macrovascular diabetes-related complications. Patients are also at risk of developing depression (new incidence case in patients with no history or current depression, relapse of depression in patients with no current depression but a history of depression), remain depressed (for patients with current depression) or depression-free (for patients with no history or current depression). It is assumed that individuals with a diabetes related complication would be more likely to develop depression compared to individuals without a diabetes-related complication. Of note, individuals are assumed to carry the impact of their complications on costs, and quality of life for life, but the impact of their complication on depression is a one-off effect during the first year after onset of the complication, as it is presumed that patients will become more accepting of their health status over time, and they will become less likely to develop depression over time. For instance, individuals experiencing an MI have an elevated risk of depression during the year of event compared with individuals who never experienced an MI, but in subsequent years there is no elevated risk of depression. In the

economic model, mortality is affected by the presence of diabetes-related complications, and diabetes-related risk factors.

Over time, patients with T2DM may or may not attend screening for depression (during the annual review or opportunistically), may or may not be diagnosed with depression, and may or may not receive depression treatment. Based on the discussions with the clinical advisors, and the results of the literature reviews, depressed individuals are assumed to be less likely to have their diabetes or other diabetes-related risk factors controlled and therefore more likely to develop diabetes-related complications [2;3]. In the economic model, a direct link between development of diabetes-related complications and depression was used due to the limited evidence available on the indirect impact of depression on the progression of diabetes-related risk factors.

Individuals are assumed to attend a number of primary care appointments associated with:

- the management of their depression
- the management of their diabetes and reasons other than their depression

Again, based on the discussions with the clinical advisors, and the results of the literature reviews, depressed individuals (treated or not) are assumed to be less likely to use healthcare resources (in terms of GP) for the management of their diabetes (and reasons other than their depression) compared with non-depressed individuals [4]. In contrast, patients with a history of depression are assumed to be more likely to be screened compared with individuals with no history of diagnosed depression.

Identified depressed individuals are assumed to attend some appointments for the management of their depression in terms of primary care appointments and IAPT services.

Characteristics of the population at baseline are described in section 5.7. The progression of diabetes-related risk factors for complications and diabetes-related complications are described in sections 5.8.1 and 5.8.2 respectively. The depression screening, case-finding, depression progression and depression treatment sub-models are described in sections 5.9, 5.10, 5.11.1 and 5.11.3 respectively. Finally the link between depression and diabetes-related complication is described in section 5.12. Parameters used in the economic model are summarised in Table 10.

**Table 10: Summary of parameters used within the economic model**

| Parameters | Basecase | References |
|---|---|---|
| Time horizon | 1 year, 10 years, lifetime | |
| **Discount rate** | | |
| Costs<br>Benefits | 3.5%<br>3.5% | NICE[5] |
| **Baseline characteristics** | See section 5.7 | |
| **Progression of diabetes-related risk factors for complications** | Assumed constant | |
| **Risk of diabetes-related complications** | | |
| Congestive heart failure (CHF) | See Appendix 8 | Hayes et al (2013)[6] |
| Ischaemic heart disease (IHD) | See Appendix 8 | Hayes et al (2013)[6] |
| Myocardial infarction (MI), first and second | See Appendix 8 | Hayes et al (2013)[6] |
| Stroke, first and second | See Appendix 8 | Hayes et al (2013)[6] |
| Blindness | See Appendix 8 | Hayes et al (2013)[6] |
| Diabetes ulcer | See Appendix 8 | Hayes et al (2013)[6] |
| Amputation (of any sort); first and second | See Appendix 8 | Hayes et al (2013)[6] |
| Renal failure | See Appendix 8 | Hayes et al (2013)[6] |
| Hypoglycaemia | 1.31% (no depression)<br>2.24% (depressed) | Katon et al (2013)[7] |
| **Risk of mortality** | See Appendix 8 | Hayes et al (2013)[6] |
| **Probability of opportunistic screening** | | |
| No history of depression<br>History of depression | 5%<br>20% | Assumption |
| **Probability of attending annual diabetes review** | | |
| No depression<br>Minor depression<br><br><br>Major depression | 90.4%<br>RR: 0.9 (no depressed vs. minor)<br>RR: 0.65 (no depressed vs. major) | QOF 2012/13 [8] DM29 indicator for non-depressed individuals<br><br>Assumptions for minor and major depression |
| **Probability that the annual review includes a depression screen** | 85.9% | QOF 2012/13 [8] DEP1 indicator |
| **Average annual number of GP appointments (other than appointments associated with depression treatment)** | | |
| Diabetes, no depression<br>Diabetes with minor depression<br>Diabetes with major depression | 12.5<br>8<br>8 | Bhattarai *et al* (2013)[9] for non-depressed individuals |

| | | |
|---|---|---|
| | | Assumption for depressed individuals |
| **Effectiveness of screening** | | |
| Sensitivity of Whooley questions<br>Specificity of Whooley questions | 95%<br>66% | NICE CG91[10] |
| **Effectiveness of the structure interview** | 100% | Assumption |
| **Incidence depression in patients with diabetes (for patients with no history of depression)** | | |
| Minor<br>Major | 5.4%<br>5.4% | Assumption for minor depression<br>Nefs et al (2012)[11] for major depression |
| **Time to progression (years)**<br>Minor to major depression | 42% at 2 years | Bot et al (2010)[12] |
| **Time to spontaneous recovery (years)**<br>Minor<br>Major | <br>0.354<br>0.877 | <br>NICE CG90 [13]<br>Spijker et al (2002)[14] |
| **Time to relapse of depression; patients with a history of depression not currently depressed (years)** | | |
| Minor<br>Major | 1.359<br>1.359 | Assumption for minor<br>Lustman et al (2006) [15]for major |
| **Duration of treatment for completers** | | |
| Watchful-waiting<br>Antidepressant<br>Low intensity psychotherapy<br>High intensity psychotherapy | 2 weeks<br>8 weeks<br>22 weeks<br>37 weeks | Assumption for watchful-waiting<br>Tosh et al (2013) [16] |
| **Waiting list** | | |
| Watchful-waiting<br>Antidepressant<br>Low intensity psychotherapy<br>High intensity psychotherapy | 0<br>7 days<br>21.8 days<br>21.8 days | Assumption for antidepressant<br>Richards et al (2010)[17] for psychotherapy |
| **Current pathway of care for depression in England** | | |
| Treatment received at step 1 in England<br>Treatment received following treatment received at step 1 | See section 5.11.2 | |
| **Response/remission** | | |
| Probability of remission under no treatment | 20% | NICE CG91 [18] |
| Relative risk for response to treatment; pharmacotherapy (minor depression) | 1.01 | NICE CG90 [18] |
| Relative risk for response to treatment; low-intensity psychotherapy (minor depression) | 1.16 | NICE CG90 [18] |
| Odds ratio for response to treatment; pharmacotherapy (major depression) | 2.5 | Baumeister (2012)[19] |

| | | |
|---|---|---|
| Odds ratio for response to treatment; low-intensity psychotherapy (major depression) | 2.88 | Baumeister (2012)[19] |
| Probability of responding to pharmacotherapy (minor/major) | 20.18% / 38.46% | Derived from the above |
| Probability of responding to low-intensity psychotherapy (minor/major) | 22.81% / 41.86% | Derived from the above |
| Relative risk for response for high-intensity compared to low-intensity psychotherapy | 2.25 | Tosh *et al* (2013) [16] |
| Probability of responding to high-intensity psychotherapy (minor/major) | 44.14% / 61.83% | Derived from the above |
| Relative risk for response for collaborative care (compared to standard practice) | 1.33 | Huang et al (2013).[20] |
| **Probability of dropping-out (minor/major)**<br>Pharmacotherapy<br>Low-intensity psychotherapy<br>High- intensity psychotherapy | <br>31.55%/31.55%<br>30.00%/30.00%<br>30.00%/30.00% | NICE CG90 [18]<br>Baumeister (2012)[19]<br>Assumption |
| **Watchful waiting: probability of dropping-out**<br>Minor<br>Major | <br>10%<br>35% | Assumption |
| **Collaborative care** | | |
| Relative risk of not dropping out of treatment (compared to usual practice) | 1.79 | Huang et al (2013).[20] |
| **Bi-directional relational depression and diabetes related complication** | | |
| Hazard ratio for developing depression due to having a microvascular diabetes-related complication<br>Minor<br>Major | <br>1.5<br>1.5 | Assumption |
| Hazard ratio for developing depression due to having a macrovascular diabetes-related complication<br>Minor<br>Major | <br>1.5<br>1.5 | Assumption |
| Hazard ratio for developing a microvascular diabetes-related complication due to having depression<br>Minor<br>Major | <br>1.31<br>1.36 | Lin et al (2010)[2] |
| Hazard ratio for developing a macrovascular diabetes-related complication due to having depression<br>Minor<br>Major | <br>1.00<br>1.25 | Lin et al (2010) [2] |
| **Health state utilities** | | |
| Baseline | 0.807 | Alva et al (2013)[21] |
| Decrements | | |
| age | -0.144 | Alva et al |

| | | |
|---|---|---|
| | | (2013)[21] |
| MI (year before) | -0.065 | Alva et al (2013)[21] |
| MI (prior history) | 0.008 | Alva et al (2013)[21] |
| IHD | -0.028 | Alva et al (2013)[21] |
| Stroke | -0.165 | Alva et al (2013)[21] |
| Heart Failure | -0.101 | Alva et al (2013)[21] |
| Amputation | -0.172 | Alva et al (2013)[21] |
| Blindness | 0.033 | Alva et al (2013)[21] |
| Renal failure | -0.263 | Klarenbach et al (2011) [22] |
| Foot ulcer | -0.016 | Sollie et al (2010)[23] |
| Severe Hypoglycaemia | -0.00186 | Marrett et al (2011)[24] and Solli et al (2010)[23] |
| Minor depression | 0 | Kaltenthaler et al (2006) [25] |
| Major depression | -0.3 | Kaltenthaler et al (2006) [25] |
| Effect of being on depression treatment on the decrement for major depression; responders only (multiplier) | x0.5 | Assumption |
| **Resource use** | | |
| Annual review | 1 primary care appointment | Assumption |
| Structured interview | 1 primary care appointment | Assumption |
| Number of primary care appointments for patients with diabetes and no depression | 12.5 | Bhattarai et al (2013) [9] |
| Number of primary care appointments for patients with diabetes and depression (other than treatment for depression) | 8 | Assumption |
| Number of primary care appointment for patients on antidepressant (initial treatment) | 3 if complete (responder/non-responder)<br>1 if drop out | Tosh et al (2013) [16] |
| Number of primary care appointment for patients receiving watchful-waiting (completers) | 2 if complete (responder/non-responder)<br>1 if drop-out | Assumption |
| Number of low intensity psychotherapy session for completers responder/non- | 3 IAPT +1 assessment<br>2 primary care | Tosh et al (2013) [16] and |

| | | |
|---|---|---|
| responder) | appointments | assumption |
| Number of low intensity psychotherapy session if drop out | 1 IAPT +1 assessment<br>1 primary care appointment | Tosh et al (2013) [16] and assumption |
| Number of high intensity psychotherapy session for completers responder/non-responder) | 7 IAPT +1 assessment<br>2 primary care appointments | Tosh et al (2013) [16] and assumption |
| Number of high intensity psychotherapy session if drop out | 3 IAPT +1 assessment<br>1 primary care appointment | Tosh et al (2013) [16] and assumption |
| **Unit costs** | | |
| Annual review | £397 | NAO [26] |
| GP appointment (lasting 11.7 minutes) | £37 | PSSRU [27] |
| GP appointment (lasting 17.2 minutes) | £55 | PSSRU [27] |
| Opportunistic screening for depression | £2 | Assumption |
| Antidepressants (daily costs) | £0.072857 | Tosh et al (2013) [16] |
| IAPT per session | £88 | Tosh et al (2013) [16] |
| **Cost of depression treatment** | | |
| Antidepressant treatment (completers) | £115.08 | Based on resource use and unit costs |
| Antidepressant treatment (drop out) | £57.54 | Based on resource use and unit costs |
| Low intensity psychotherapy (completers) | £426 | Based on resource use and unit costs |
| Low intensity psychotherapy (drop out) | £213 | Based on resource use and unit costs |
| High intensity psychotherapy (completers) | £778 | Based on resource use and unit costs |
| High intensity psychotherapy (drop out) | £389 | Based on resource use and unit costs |
| **Diabetes-related complications** | | |
| Diabetes – no complications | £252[a] | Clarke et al (2003)[28] |
| CHF – year of event | £3,559[a] | Clarke et al (2003)[28] |
| IHD – year of event | £3,139[a] | Clarke et al (2003)[28] |
| MI – year of event | £6,522[a] | Clarke et al (2003)[28] |
| Stroke – year of event | £3,793[a] | Clarke et al (2003)[28] |
| Blindness – year of event | £1,397[a] | Clarke et al (2003)[28] |

| | | |
|---|---|---|
| Ulcer – year of event | £1,855 [a] | Ghatnekar et al (2002) [29] |
| Amputation – year of event | £13,556 [a] | Clarke et al (2003)[28] |
| Renal failure – year of event | £34,806 | NICE STA for dapagliflozin[30] |
| CHF – subsequent years | £1,011 [a] | Clarke et al (2003)[28] |
| IHD – subsequent years | £790 [a] | Clarke et al (2003)[28] |
| MI – subsequent years | £744 [a] | Clarke et al (2003)[28] |
| Stroke – subsequent years | £399 [a] | Clarke et al (2003)[28] |
| Blindness – subsequent years | £450 [a] | Clarke et al (2003)[28] |
| Ulcer – subsequent years | £21 [a] | Ghatnekar et al (2002) [29] |
| Amputation – subsequent years | £481 [a] | Clarke et al (2003) [28] |
| Renal failure – subsequent years | £34,806 | NICE STA for dapagliflozin[30] |
| Severe hypoglycaemia | £390 | NICE STA for dapagliflozin[30] |
| **Societal impact** | | |
| Number days off work | See section 5.15 | EEPRU [31] |
| Informal care | See section 5.15 | EEPRU [32] |
| **Cost associated with Collaborative Care** | | |
| Antidepressant (completers) | £85 | NICE CG91[10] |
| Antidepressant (drop out) | £43 | |
| Low intensity psychotherapy (completers) | £142 | NICE CG91[10] |
| Low intensity psychotherapy (drop out) | £71 | Assumption |
| High intensity psychotherapy (completers) | £240 | NICE CG91[10] |
| High intensity psychotherapy (drop out) | £120 | Assumption |

[a]uplifted to 2013[27;33]

### 5.2 Target population

The population considered in the economic model is adults with diagnosed T2DM in England. A strict definition of 'adult' was not employed, it was noted that this could vary between evidence sources. For example, age-ranges of seventeen and older or eighteen and older were used. Neither antenatal diabetes nor inpatient diabetes was specifically considered for this work. The focus of the project was England and patients could have existing depression, develop depression, or remain depression-free.

### 5.3 Study perspective

The analysis takes the perspective of the UK National Health Service and personal social services. A wider societal perspective was explored, considering the impact on productivity (in terms of days off work due to ill-health) and informal care (days received any unpaid care provided by family or friends). Further details are provided in section 5.16.

### 5.4 Time horizon and discounting

A lifetime horizon was used to ensure that all differences in costs and benefits were captured within the economic model. Both costs and QALYs were discounted at a rate of 3.5 per cent per year, as recommended by the National Institute for Health and Care Excellence (NICE) in England.[34]

### 5.5 Model results

The economic model considers a cohort at baseline with diagnosed T2DM in England and follows this cohort until death. The inflow of newly diagnosed T2DM over time (e.g. new cohort every year) was not considered.

Results are reported at the population level, assuming a population size of 2,000,000 patients with diagnosed T2DM in England at baseline.[35] Results are presented for a lifetime horizon.

The following outcomes, process measures and costs are considered:

- Number of microvascular complications
- Number of macrovascular complications
- Number of depression episodes, identified, treated, unidentified
- Number of primary care appointments for the management of depression

- Number of primary care appointments (for reasons other than the management of depression)
- Number of IAPT appointments (low and high intensity)
- Number of patients screened through the annual screening
- Number of patients screened opportunistically
- Number of structured diagnostic interviews performed
- Number of years with and without depression
- Number of patients treated for depression
- Number of patients with depression over time
- Number of patients with a history of depression over time
- Number of days off work due to ill-health
- Number of days received any unpaid care provided by family or friends
- Life years (discounted and undiscounted)
- QALYS (discounted and undiscounted)
- Diabetes-related costs for the management of diabetes-related complications
- Primary care costs for the management of diabetes
- Primary care costs for the management of depression
- Opportunistic screening costs
- Costs associated with structured diagnostic interviews

Univariate sensitivity analyses were conducted to explore the robustness of results to variations in key parameters, and in particular where assumptions were required. The analyses which have an effect on results are presented and described in narrative format.

### 5.6 Programming of the economic model

The economic model was informed by two published existing economic models:

- The UKPDs OMv2 for diabetes-related risk factors and diabetes-related complications[6]
- Tosh et al (2013) for the natural history and treatment/management of depression [16]

These two models have been reconstructed based on the information available [6;16], and adapted to include elements that were deemed essentials by advisors and service users at the conceptual model stage and to reflect the scope of this project (Section 4).

The model uses a discrete-event simulation (DES) approach (i.e. time to event). An individual-based model was used instead of a state-transition model primarily because of the large number of patient characteristics that require tracking over time. Of note, the UKPDS model [36] evaluates outcomes on an annual basis whilst Tosh *et al*. (2013) [16] uses a time to event approach. To incorporate evidence from the UKPDS model into the DES structure of the current model, complications/risk factor progression were treated as annual events, so that they had a fixed time-to-event of one year before they were evaluated.

Times to events are sampled from statistical distributions. To estimate the probability of diabetes-related complications from the UKPDS, a probability of experiencing one or more complications is calculated for each patient based on the UKPDS risk equations. The calculated probabilities are then compared with a random number drawn from a uniform distribution ranging from zero to one to determine whether an event actually occurs for this patient. In the UKPDS model, risk equations for complications are executed in random order (i.e. equations are executed sequentially, but with a different order every time); and events in a given cycle inform the probability of experiencing further events within the same cycle.

As highlighted in NICE CG87 [37], due to the patient-level approach of the UKPDS, a large number of iterations of the model have to be run in order to reduce the variability within the estimates and achieve convergence for the point estimates. In the model informing NICE CG87 [37], 250,000 iterations were performed; however, there remains small variability across estimates. Although the basecase for current practice appeared to converge below 50,000 iterations, due to the relatively small effect from the policies explored, the number required for convergence increased substantially when comparing policies and looking at

incremental values. Due to computational availability for this project, 600,000 iterations were run. However, it is likely that some variability may remain and this should be borne in mind when interpreting the results.

### 5.7 Characteristics of the population included at baseline in the economic model

The economic model reflects the characteristics of individuals with T2DM currently managed in England. Baseline characteristics in terms of demographics (such as age, gender), clinical/diabetes-related risk factors (such as HbA1c, blood pressure) and presence/absence of diabetes-related complications were required.

Baseline characteristics were sourced from the National Diabetes Audit (NDA)[35] when available. In England, the NDA is commissioned by the Healthcare Quality Improvement Partnership (HQIP) and reports indicators on key care processes and treatment target achievement rates (measures the effectiveness of diabetes healthcare against NICE Clinical Guidelines and NICE Quality Standards) in England and Wales. The audit collects information from both primary and secondary care; with the vast majority of cases registered in primary care (≈98%). The latest published NDA audit included 2,473,239 individuals (from 87.9% of practices across England and Wales) with diabetes (T1DM and T2DM) from 1st January 2011 to the 31st March 2012 and 2,216,129 individuals with T2DM from 1st January 2011 to the 31st March 2012.[35]

The NDA reports a variety of information and the economic model used the NDA data for age, duration of diabetes, gender, ethnicity, smoking status and BMI. As the NDA reports the distribution of age using 10 year age-bands, patients aged 19 years old or less were excluded. A normal distribution was fitted to the remaining data, assuming constant distributions within categories to estimate the mean age (see Appendix 9 for details of the calculation). It was assumed that baseline characteristics were similar between England and Wales.

The NDA also reports odd ratios to assess the risk of having diabetes-related complications (CHF, IHD, MI, stroke, blindness, amputation, renal failure) according to patient characteristics. These odd ratios were used in the economic model to calculate the history of diabetes-related complications for patients entering the model at baseline (see Appendix 10 for details).

UKPDS baseline characteristics (description available in Appendix 11) were used when evidence was not available from the NDA for HbA1c, BMI, SBP, high-density lipoprotein (HDL), low-density lipoprotein (LDL), white blood cell (WBC), haemoglobin, heart rate, epidermal growth factor receptor (eGFR), presence of micro/macro albuminuria, atrial fibrillation (AF) and peripheral vascular disease (PVD).

Of note, patients included in the UKPDS may not be representative of the population with T2DM currently managed in England as the UKPDS trial commenced 20 years ago, and only included patients with newly diagnosed diabetes. Patients were also a selected population (younger population, with no recent history of CHF, MI or IHD).

In addition to these baseline characteristics, the following prevalence rates were required for the economic model at baseline:

- Prevalence of individuals with no history of depression (and no current depression)
- Prevalence of individuals with a history of depression but no current depression
- Prevalence of individuals with "current" minor depression on treatment
- Prevalence of individuals with "current" major depression untreated.

Neither the NDA nor the UKPDS reported the prevalence of individuals with T2DM who have depression in England. Instead, data were used from a study carried out in England. Based on an electronic hospital database, out of 4,781 patients with T2DM, 435 (9.3%) had depression. Depression was based on either case documentation or use of antidepressant medication at the therapeutic dose, so is likely to relate to major depression. No English data were available on the prevalence of minor depression (either amongst individuals with T2DM or amongst the general population), so it was assumed that this was the same as the prevalence of major depression. Hence for the economic model, 9.3% of individuals had major depression at baseline, and 9.3% had minor depression at baseline. This value was varied in sensitivity analyses by doubling and halving it.

It was further assumed that amongst individuals without existing depression (at baseline), 9.3% would have a history of depression. This 9.3% was split equally between minor and major depression, giving a baseline history of 4.65% for both. [38]

Finally, amongst individuals with depression at baseline a proportion will be identified (and hence treated). As no published evidence was available for these proportions, they were

assumed to increase with severity of depression. The following values for identified (treated) depression were used: 60% for minor, 80% for major. Individuals with current depression (minor or major) were assigned to treatment by assuming that they were at Step '1' of treatment (see Section 5.11.2) for more details.

A summary of the baseline characteristics and sources used in the economic model is presented in Table 11.

As the model uses an individual-based approach, baseline characteristics were sampled so that each patient entering the economic model had individual characteristics. Normal distributions were used to sample continuous variables based on the mean and standard deviation such as age, HbA1c, and blood pressure, but boundaries were applied to ensure that the sampled values were realistic. For proportions, a random number was drawn from a uniform distribution on the interval [0, 1]. This random number was then compared to the estimated proportion to determine if the individual had that characteristic at baseline.

In the absence of patient-level data, summary statistics from the NDA [35] and UKPDS [6] were used and therefore baseline characteristics were sampled independently of each other (i.e. no correlation was included). This is a limitation as there may be correlations between baseline characteristics; for instance patients with high HbA1c may be more likely to be older, with high blood pressure and high BMI.

**Table 11: Parameters used for the baseline characteristics**

| Variable | Value | Baseline distribution (moments) | Source |
|---|---|---|---|
| Mean age | 66.48±12.96 | Sampled from Normal distribution | Derived from NDA [35] |
| Mean time with T2DM | 6.37 | Assumed to be constant | Derived from NDA [35] |
| P(Female) | 0.444 | | NDA [35] |
| P(Afro-Caribbean) | 0.044 | | NDA [35] |
| P(Indian) | 0.130 | | NDA [35] |
| P(Smoke) | 0.155 | | NDA [35] |
| Mean BMI | 30.34±7.09 | Sampled from Normal distribution | NDA [35] |
| Mean HbA1c | 8.2±1.5 | Sampled from Normal distribution | UKPDS [6] |
| Mean SBP | 143±20 | Sampled from Normal distribution | UKPDS [6] |
| Mean HDL | 1.19±0.3 | Sampled from Normal distribution | UKPDS [6] |
| Mean LDL | 3±0.6 | Sampled from Normal distribution | UKPDS [6] |
| Mean Heart Rate | 72±12 | Sampled from Normal distribution | UKPDS [6] |
| Mean eGFR | 77.5±15 | Sampled from Normal distribution | UKPDS [6] |
| P(Albuminuria) | 0.17 | | UKPDS [6] |
| P(At Fib) | 0.005 | | UKPDS [6] |
| P(PVD) | 0.14 | | UKPDS [6] |
| Mean white blood cell count | 6.8±1.8 | Sampled from Normal distribution | UKPDS [6] |
| Mean haemoglobin | 145±13 | Sampled from Normal distribution | UKPDS [6] |
| CHF history | Appendix 10 | | NDA [35] |
| IHD history | Appendix 10 | | NDA [35] |
| MI history | Appendix 10 | | NDA [35] |
| Stroke history | Appendix 10 | | NDA [35] |
| Blind history | Appendix 10 | | NDA [35] |
| Ulcer history | 0.002 | | UKPDS [6] |
| Amputation history | Appendix 10 | | NDA [35] |
| Renal failure history | Appendix 10 | | NDA [35] |
| P(Minor depression) | 9.3% | | Ali et al 2009[38] |
| P(Major depression) | 9.3% | | Ali et al 2009[38] |
| P(depression is treated)<br>Minor<br>Major | <br>60%<br>80% | | Assumptions |
| P(history of minor depression) | 4.65% | | Assumption |
| P(history of major depression) | 4.65% | | Assumption |

### 5.8 Description of the diabetes sub-model

An existing diabetes mathematical model, the UKPDS OMv2[6] was reconstructed based on the information publicly available and was adapted to reflect the clinical advisors' and service users' views expressed during the conceptual modelling process. A brief description of the UKPDS OMv2 is provided in Appendix 7.

In summary, compared to the published UKPDS OMv2 [6], the following amendments were made:

- The inclusion of depression (see Sections 5.9 to 5.11)
- Different assumptions were made regarding the progression of diabetes-related risk factors (see Section 5.8.1)
- The use of different baseline characteristics (see Section 5.7)
- The inclusion of severe hypoglycaemia (see Section 5.8.2)

The diabetes sub-model is composed of three main elements:

- The progression of clinical parameters or diabetes-related risk factors for complications
- The relationship between diabetes-related risk factors for complications and the development of diabetes-related complications
- Mortality

These are discussed in turn below.

#### 5.8.1. Progression of diabetes-related risk factors for complications

Diabetes-related risk factors for the development of complication are based on those included in the UKPDS OMv2[6] with the exception of depression (see Section 5.11.1).

The diabetes-related risk factors for the development of complications can be categorised either as demographic (e.g. age, gender), clinical/biological (e.g. diabetes duration, BMI, HbA1c, blood pressure) or the presence of existing complications (e.g. previous MI, amputation).

At the time of writing of the report, the progression rates for diabetes-related risk factors for complications included in the UKPDS OMv2 were not published. Furthermore, it should be noted that patients included in the UKPDS are patients newly diagnosed with diabetes.[39]

For simplicity, progression rates for diabetes-related risk factors for complications (such as HbA1c, BMI, HDL, LDL) were assumed to be constant. Similar assumptions have been made in other diabetes models.[40] Of note, this is a limitation of the analysis and likely to underestimate the risk of developing diabetes-related complications. However, as the UKPDS includes newly-diagnosed diabetes, the risk factor progression rates estimated for this may not be applicable to the population considered for this project.

### 5.8.2. Relationship between diabetes-related risk factors for complications and the development of diabetes-related complications

The list of diabetes-related complications is primarily based on the UKPDS OMv2. Whilst weight gain and mental health (other than depression) were considered important at the conceptual stage, these were excluded from the economic model due to the lack of robust evidence. Similarly, whilst "soft" outcomes were considered at the conceptual stage (such as neuropathy, nephropathy and retinopathy), the economic model included the final outcomes such as blindness, CHF and renal failure as these were the complications included in the UKPDS OMv2.

In addition to the diabetes-related complications included within the UKPDS OMv2, severe hypoglycaemia and depression were included in the economic model as hypoglycaemia was identified during the conceptual stage (section 4) and depression was the scope of the project.

Overall, the economic model considered a total of 10 complications

1. CHF
2. IHD
3. MI, first and second
4. Stroke, first and second
5. Blindness
6. Diabetes ulcer
7. Amputation (of any sort), first and second
8. Renal failure
9. Hypoglycaemia
10. Depression

Individuals have an ongoing risk of developing a diabetes-related complication based on their diabetes-related risk factors for complications described above (e.g HbA1c, BMI, smoking).

For diabetes-related complications taken from the UKPDS OMv2 [6] the risk of developing a diabetes-related complication was taken from published regression models from the UKPDS OMv2, based on an individual's diabetes-related risk factors for complications and history of other complications. The regression models used to predict the risk of diabetes-related complication, along with a worked example, are presented in Appendix 8. Of note, the UKPDS OMv1 model [39] for renal failure was used due to issues with convergence for the later version in the UKPDS OMv2.

It was assumed that the risk equations from the UKPDS were for non-depressed individuals. However, in the economic model, depressed individuals are assumed to have an elevated risk of experiencing diabetes-related complications compared with non-depressed individuals (See section 5.12).

For severe hypoglycaemia, the systematic review did not identify any evidence. Targeted searching identified evidence from Katon et al (2013), which was used [7]. The authors reported findings from a longitudinal cohort study conducted in the US and followed 4,117 patients with diabetes enrolled between 2000 and 2002 and observed from 2005 to 2007. In this study, a severe hypoglycaemic episode was defined as an episode requiring an emergency department visit or hospitalization. The author found that depressed patients who had diabetes had a significantly higher risk of a severe hypoglycaemic episode (hazard ratio = 1.42, 95% CI, 1.03–1.96) and a greater number of hypoglycaemic episodes (odds ratio = 1.34, 95% CI, 1.03–1.74) compared with non-depressed patients who had diabetes after adjustment for sociodemographic, clinical measures, comorbidity, prior hypoglycaemic episodes, and health risk behaviours that. The authors reported that in the 5-year pre-baseline period, 8.1% of depressed patients with diabetes vs 3.1% of non-depressed control patients with diabetes experienced 1 or more severe hypoglycaemic episodes. Over the 5-year follow-up period, 6.9% of patients reported at least 1 severe hypoglycaemic episode. A total of 10.7% of depressed patients with diabetes had 1 or more severe hypoglycaemic episodes, compared with 6.4% among non-depressed control patients.

Based on the estimate from Katon et al (2013),[7] an annual incidence of 1.31% for severe hypoglycaemia (1 or more episodes) was assumed for non-depressed individuals and 2.24% for depressed individuals.

The risk of developing depression is estimated using the depression sub-model (see Section 5.11) and is derived from published sources and assumptions when appropriate. This includes the probability of developing new depression (for individuals with no history of depression) or relapse of depression (for individuals with a history of depression).

### 5.8.3 Risk of mortality

Individuals in the model have an ongoing risk of death from diabetes-related complications and from other causes (all-cause mortality).

The risk of death is taken from the UKPDS OMv2[6] and calculated using four different regression models:

- whether or not an individual has a history of diabetes-related complications
- current diabetes-related complications
- whether or not an individual has a history of diabetes-related complications and current complications
- all-cause mortality (amongst individuals with diabetes and no diabetes-related complications).

The UKPDS regression models used to predict mortality are presented in Appendix 8. These predict all-cause mortality for a population with diabetes, with separate equations which take into account the increased risk for diabetes related complications and risk factors.

### 5.9 Depression screening

As previously described at the conceptual stage (section 4), there are three ways of screening: spontaneous presentation when the individual presents with symptoms of depression, opportunistically (appointment unrelated to depression), and through the annual diabetes review. Following discussions with advisors and the evidence review, spontaneous presentation and opportunistic screening were combined in the economic model for simplicity and to accommodate evidence available.

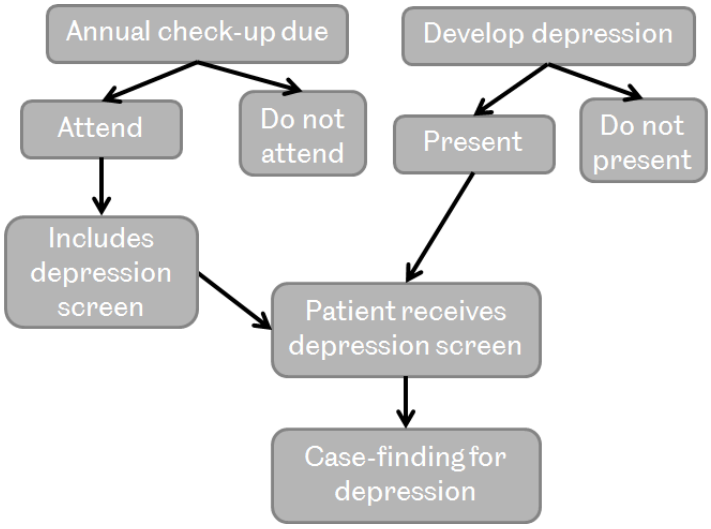
Consequently, there are two routes by which an individual may receive a depression screen in the economic model:

a) as part of their annual diabetes review
b) opportunistically, as part of a routine primary care appointment including spontaneous presentation due to symptoms of depression

If individuals receive a screen as part of their annual diabetes check-up, they immediately move to the '*depression case-finding*' sub-model.

A schematic of how depression screening is implemented in the economic model is provided in Figure 10.

**Figure 10: Schematic of the depression screening sub-model**




A summary of the evidence used for depression screening in the economic model is provided in Table 12.

**Table 12: Evidence on screening used within the economic model**

| | | |
|---|---|---|
| **Probability of attending annual diabetes review**<br>• No depression<br>• Minor depression<br>• Major depression | 90.4%<br>RR*: 0.9 (no depressed vs. minor)<br>RR*: 0.65 (no depressed vs. minor) | QOF 2012/13 [8]<br>DM29 indicator<br>Assumptions for minor and major depression |
| **Probability that the annual review includes a depression screen** | 85.9% | QOF 2012/13 [8]<br>DEP1 indicator |
| **Average annual number of GP appointments (other than appointments associated with depression treatment)**<br>• Diabetes, no depression<br>• Diabetes with minor depression<br>• Diabetes with major depression | 12.5<br>8<br>8 | Bhattarai *et al* (2013) [9] for non-depressed individuals<br>Assumptions for depressed individuals |
| **Probability that a GP appointment includes a depression screen**<br>• No history of depression<br>• History of depression | 5%<br>20% | Assumption |
| **Effectiveness of screening**<br>Sensitivity of Whooley questions<br>Specificity of Whooley questions | 95%<br>66% | NICE CG91 [10] |

** RR<1 indicate patients are less likely to attend the annual diabetes review. RR: Relative risk*

### 5.9.1 Annual diabetes review

Within the health economic model, the annual diabetes review occurs once a year. Individuals have a probability of attending the review and this probability varies depending on the individuals' depression status (i.e. whether the individual is depressed or not). If individuals attend the review, there is a probability that the review would include a depression screen. If the individual has depression that was already identified, then the annual diabetes review would not include a depression screen.

The following parameters were required for the economic model relating to the annual diabetes review:

- Probability of an individual attending their annual diabetes review (by depression status)
- Probability that the review includes a depression screen

*Probability of an individual attending their annual diabetes review (by depression status)*

National data on participation and outcomes of the annual review for patients with T2DM in the UK are publically available via the QOF.[8] The QOF is a voluntary incentive scheme for GP practices in the UK and contains groups of indicators. Discussions with clinical advisors indicated that the indicator for foot examination and HbA1c measurements were specific to diabetes, and these are usually performed during the annual review. Consequently, the English average achievement rate for diabetes indicator 29 (DM 29: the percentage of patients with diabetes with a record of a foot examination and risk classification) was used in the basecase to approximate the probability of attending an annual diabetes review. Based on the latest publically available QOF (April 2012 - March 2013), 90.4% of patients with diabetes had a foot examination (DM29).

It was believed that the probability of attending the annual review was likely to vary by depression status. For example Gonzalez *et al* [4] showed a statistically significant association between depression and appointment keeping. Unfortunately, the QOF does not provide a breakdown (against diabetes indicators) by depression status.

Due to the lack of evidence, assumptions were made. It was assumed that the probability of patients attending the annual review was 90.4% for patients with no depression, based on the QOF indicator for foot ulcers.[41] This is likely to be an underestimate as this value includes a mix of depressed and non-depressed individuals. It was further assumed that patients with minor and major depression were 10% and 35% less likely to attend the annual review compared with patients with no depression respectively. These values were varied in a sensitivity analysis which assumed that everybody attended the annual diabetes review and received a depression screen.

*Probability that the review includes a depression screen*

The probability that an annual review includes a depression screen was taken from the depression indicator (DEP1) of the QOF ("The percentage of patients on the diabetes register and /or the CHD register for whom case finding for depression has been undertaken on one occasion during the preceding 15 months using two standard screening questions")[8]. Clinical advisors indicated that within the QOF, GPs have the option to exclude patients from an indicator if they have reason to believe that the indicator is not applicable or appropriate. Excluding these exceptions, the achievement rate for the indicator DEP1 was 85.9% and this value was used in the economic model. A sensitivity analysis was conducted using a value of 60%.

### 5.9.2 Opportunistic screen

An opportunistic screen for depression is defined as a screen that is carried out by a healthcare professional during an appointment that was not scheduled to include a depression screen. This can be either because the patient presents with symptoms of depression or as part of visit to the GP for other reasons.

In the economic model, it is assumed that individuals attend a number of primary care appointments (for any reason) every year, according to their depression status (depressed vs. non-depressed). These primary care appointments can be with a variety of primary care staff, such as a GP, practice nurse or diabetes nurse.

Unless the individual has already been identified with depression, it is assumed that there is a probability that the primary care appointment will include an opportunistic screen. If so, then the individual immediately moves to the "*depression case-finding"* sub-model.

The following parameters were required for the economic model:

- Number of primary care appointments (by depression status)
- Probability of a primary appointment includes a depression screen (according to history of depression)

*Number of primary care appointments (by depression status)*

The average number of primary care appointments per year was taken from Bhattarai *et al* (2013).[9] The authors used data from the UK General Practice Research Database (GPRD), which covers approximately 6% of all GPs (approximately 5 million patient records) in the UK (2005-2009) and included only patients aged between the ages of 30 to 100 years old. The authors reported the number of GP practice consultation (including family practice consultations, telephone consultations, home visits, emergency and out-of hours consultations) per year for patients with just diabetes,, diabetes and CHD, diabetes and stroke, CHD and stroke for males and females separately. These are presented in Table 13. Depression presence was identified if individuals had a READ code for depression recorded in the year of interest, or if they were ever diagnosed with depression and had a prescription of antidepressants recorded in the year of interest.

**Table 13: Age standardized rates per person-year for primary care consultations**

| | DM only | | DM and CHD | | DM and stroke | | DM, CHD and stroke | |
|---|---|---|---|---|---|---|---|---|
| | **Male** | **Female** | **Male** | **Female** | **Male** | **Female** | **Male** | **Female** |
| Non-depressed | 12 (6-18) | 13 (7-19) | 16 (9-24) | 17 (11-24) | 18 (8-27) | 20 (11-29) | 19 (10-28) | 22 (12-32) |
| Depressed | 19 (11-27) | 19 (12-26) | 22 (13-30) | 24 (16-32) | 26 (15-38) | 24 (16-33) | 24 (13-35) | 22 (15-29) |

reproduced from Bhattarai et al, 2013

The study did not present average number of appointments for all patients irrespective of presence of complications. The study also considered both T1DM and T2DM. Based on this study [42], in the economic model, it was assumed that non-depressed individuals attend 12.5 primary care appointments a year (e.g. about one primary care appointment per month) for their management of diabetes and other causes.

For depressed individuals, the value reported by Bhattarai et al (2013) [42] included primary care appointments associated with the treatment of depression. As these are included separately in the economic model, using the value from the Bhattarai study would be double counting the number of primary care appointments.

It was believed that individuals with diabetes and depression are less likely to attend primary care appointments than individuals with who have diabetes but do not have depression (excluding appointments associated with their depression treatment). Consequently, in the basecase, it was assumed that individuals with minor and major depression had 8 primary care appointments a year (other than those associated with their management of depression); i.e. a reduction of around 35% of attending primary care appointments (other than for their management of depression) compared with non-depressed individuals. This was varied in two sensitivity analyses, one of which used the same value for diagnosed and undiagnosed depression and one of which set the annual number of primary care appointments for depressed individuals to be 4.

*Probability that a primary care appointment includes a depression screen*

No study was identified which provided evidence on the probability that a primary care appointment includes an opportunistic screen. Clinical advisors suggested that there is wide variation in practice and that this usually depends on whether the patient had a known history of depression.

In the basecase, it was assumed that 5% of GP appointments included a screen for patients with no history of depression. The probability for individuals with a history of depression was assumed to be 20% in the basecase. These values were varied in sensitivity analysis by doubling and halving them.

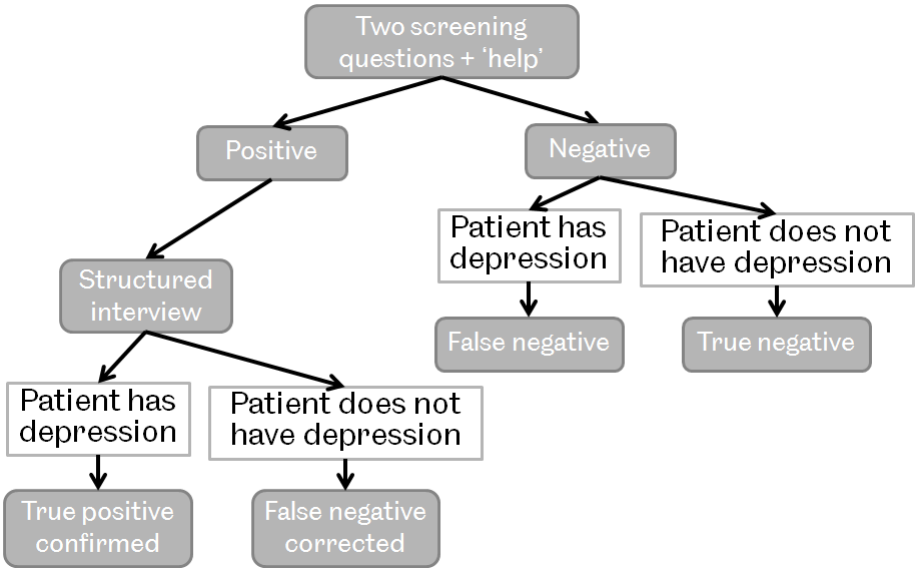
### 5.10 Depression case-finding

An important aspect of the economic model is the inclusion of individuals with untreated depression. Screened individuals (entering the depression case-finding sub-model) can either receive a positive or negative screening for depression. However, the screening tool is not 100% perfect (as measured by the sensitivity and specificity of the test) and therefore misclassification is possible.

In the model, individuals with depression and a positive screen result are defined as 'true positive', whilst individuals with depression and a negative screen result are defined as 'false negative'. Individuals without depression and a positive screen result are defined as 'false positive', whilst individuals with no depression and a negative screen result are defined as 'true negative'. The probability that an individual with depression experiences a positive screen result is known as the sensitivity of the screening test, whilst the probability that an individual without depression experiences a negative screen result is known as the specificity of the screening test.

A schematic of the depression case-finding sub-model used within the economic model is provided in figure 11.

**Figure 11: Schematic of the depression case-finding sub-model**




Within the model, the effectiveness of screening (as measured by sensitivity and specificity) determines whether or not an individual's depression is identified. No further action is assumed for individuals receiving a negative screen result, whilst a follow-up structured interview is performed for individuals who screen positive. The role of the follow-up structured interview is to either confirm cases of depression (amongst people with depression) or correct cases of incorrectly identified depression (amongst people without depression). The possible outcomes for this sub-model are summarised in Table 14.

**Table 14: Possible outcomes for the depression case-finding sub model**

| | Initial screen negative | Initial screen positive |
|---|---|---|
| Individual does not have depression | True negative, no further action. | False positive, individual has follow-up structured interview to change this to a true-negative. |
| Individual has depression | False negative, no further action. Individual has unidentified (and hence untreated) depression. | True positive, individual enters the depression treatment sub-model. |

The following parameters were required for the economic model:

- Effectiveness (sensitivity and specificity) of screening for depression
- Effectiveness of the structured interview

An overview of the evidence used in the economic model is provided in Table 15.

**Table 15: Screening and case-finding evidence used within the economic model**

| | Value | Source |
|---|---|---|
| Sensitivity of Whooley questions | 95% | NICE CG91 [10] |
| Specificity of Whooley questions | 66% | NICE CG91 [10] |
| Effectiveness of the structure interview | 100% | Assumption |

*Effectiveness (Sensitivity and specificity) of the Whooley questions*

As described in the conceptual model (section 4) patients are screened for depression using the Whooley questions, along with an additional 'help' question (as recommended in the QOF) [8]. Two meta-analysis of the effectiveness of screening tools for depression in adult with a chronic physical condition (not specifically diabetes) were identified [18;43]. The meta-analysis conducted by NICE CG91 [10] included 7 studies considering the Whooley questionnaire. The following databases were searched from inception to February 2009: MEDLINE, EMBASE, PsycINFO, Cochrane Library. Using meta-analysis, the authors estimated the sensitivity and specificity of the Whooley questions to be 95% and 66% respectively. This was used in the basecase economic model.

The meta-analysis conducted by Meader et al (2011) [44] appears to be an update of the NICE CG91[10], but report findings for the 2-stem questions instead of Whooley questionnaire. It is unclear whether studies using the Whooley questionnaire were included. References of included studies were also different between the 2 studies [10;44]. A sensitivity analysis was conducted using the calculated sensitivity (98%) and specificity (86%) of the two stem questions.

*Effectiveness of the structured interview*

It was assumed that the diagnostic interview would confirm all (screen-positive) cases of depression (if depression is present), whilst correcting all cases of no depression that screened positive (if depression is absent). This is a simplification of the effectiveness of a structured interview, as it assumes that both sensitivity and specificity are both 100%, which is unlikely to be true in clinical practice. However, clinical advisors felt that these assumptions were appropriate as the main area of interest for the depression case-finding sub-model is the amount of unidentified depression and the impact on patients not receiving treatment.

### 5.11 Depression progression (natural history of depression)

Informed by the conceptual model, depression was categorised into two health states depending on the severity: minor (also known as sub-threshold) and major. Depression was included in the economic model as categories instead of as a continuous measure due to a lack of data for the latter. Two different health states (minor and major) were used as, based on clinical advice, it was decided that this represented a suitable compromise between representing the different aspects of depression in sufficient detail and having sufficient detailed evidence for each of the categories. Following a review of the evidence, it was decided to not consider transitions between the different states of major depression (mild, moderate, severe) as evidence was lacking for both progression between the health states and the effects of any policy changes on improving depression severity. Evidence was also lacking on the type of major depression for incidence and relapse.

Similarly, due to the evidence available, the conceptual model for depression progression (section 4) was simplified as follows:

- No distinction was made between response, remission and recovery. Within the economic model these are all termed 'recovery'.
- No distinction was made between relapse and recurrence. Within the economic model these are both termed 'relapse'.
- No distinction is made between depressive episodes and persistent depression. The term 'depressive episode' is used within the economic model.
- 'Normal mood' is referred to as 'No depression' within the economic model, and is sub-divided depending on whether or not the individual has a history of depression.
- Death from depression was not directly included; however, depression increases the risk of diabetes-related complications, which in turn increase the risk of death.

In the economic model, time to minor or major depression for patients with no history of depression (giving time to incidence) or history (giving time to relapse) of depression was sampled (for example sampled times may be 4 months for minor and 9 months for major). The time to first event (which in this example would be e.g. minor depression) is used to define the start (in this example it would be time now+4 months) and severity of depression (which in this example would be e.g. minor depression). A time to recovery (for example 7 months) was then sampled for this minor episode only. If the time to major depression was shorter than the sampled time to recovery plus time at which the episode started (which in this example is 11 months), then the individual is assumed to have minor depression for a

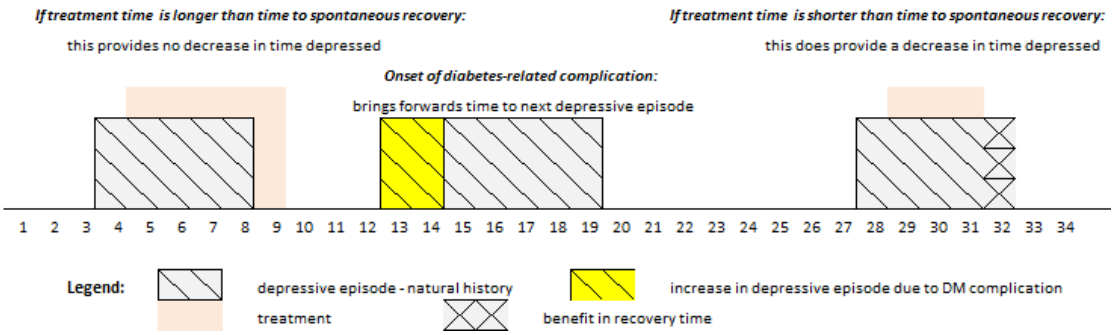
certain amount of time, and major depression for the remaining time before recovery. If the sampled time to major depression was greater than the sampled time to recovery, the individual is assumed to have only an episode of minor depression until spontaneous recovery.

Similarly, if the time to major depression was shorter than the time to minor depression, it is assumed that the individual would develop major depression first and would have minor depression the remaining time (unless they recover in the time period between their sampled time to major depression and their sample time to minor depression).

In general time-to-event data for the natural history of depression were based on events at a single time-point. For example, for the incidence of depression a value of 13% at 2.5 years was used. When only single time-points were used, it was assumed that the events occurred at a constant rate over time, and so an exponential distribution was used. The one exception was time-to-recovery for major depression, for which a Weibull distribution was fitted to a published survival curve. [14]

A schematic of the logic is presented in Figure 12. In this example, the episode of depression is minor. If the sampled time to major depression is equal to the red arrow (about 4 months), and recovery is 3 months after the start of the depression episode, the individual remains one month in the minor depression health state and the remaining time in the major depression health state. On the other hand, if the sampled time to major depression is equal to the purple arrow (e.g. about 6 months), the individuals is assumed to have minor depression for 4 months until recovery.

**Figure 12: Example of time to depression**



Individuals may experience multiple episodes of depression within a year. In the economic model, individuals with no history of depression can either develop depression (minor, major) or remain depression-free. Individuals with a history of depression (but no current depression) can either relapse or remain depression free. Finally, individuals with current depression can either recover (move to 'no depression') or remain depressed.

The depression progression sub-model considers the natural history of depression assuming no treatment is received. This includes the incidence of depression (new cases with no history of depression), spontaneous recovery, and relapse (for individuals with a history of depression but no current depression). It was assumed that individuals with a history of minor depression can relapse to either minor or major depression. Similarly, individuals with a history of major depression could relapse to either minor or major depression.

The natural history (progression of depression assuming no treatment) is then modified in two ways:

- Individuals treated for depression may recover faster than the sampled time to spontaneous recovery if they respond to treatment
- If an individual has a new diabetes-related complication, the individual has an elevated risk of depression episodes over the first year compared with non-depressed individuals (see Section 5.12). There is no elevated risk in subsequent years as it is assumed it is the initial effect of the complication which increases the risk of depression.

Individuals have a risk of developing depression at a specific time in the economic model (based on their natural history of depression). If individuals are treated for an episode of depression, the current episode of depression may be shortened (if the individuals responds to treatment and the length of treatment is shorter than the length of the depression episode), and the time to relapse is increased (difference between time to next depression episode and time to response to treatment for the previous episode).

### 5.11.1 Depression progression (natural history of depression)

The following parameters were required for the economic model:

- the probability of developing depression for patients with no history of depression
- time to spontaneous recovery of depression for patients with current depression not on treatment
- the probability of relapse for patients with a history of depression but no current depression

Where possible, evidence was taken from T2DM populations, but evidence from the general population was considered when no evidence was identified in diabetes specific populations. Parameters are summarised in Table 16.

**Table 16: Summary of parameters used for the natural history of depression**

| | | **Source** |
|---|---|---|
| **Time to incidence of depression for patients with no history of depression (years)** | | |
| • Minor | 5.4% per year | Assumption for minor |
| • Major | 5.4% per year | Nefs et al for major(2012) [11] |
| **Time to spontaneous recovery (years)** | | |
| • Minor | 0.354 | NICE CG90[13] |
| • Major | 0.877 | Spijker et al (2002)[14] |
| **Time to relapse of depression for patients with a history of depression, but not current depression (years)** | | |
| • Minor | 1.359 | Same as major |
| • Major | 1.359 | Lutsman et al (2006)[15] |

- *Incidence of depression (amongst individuals with no history of depression)*

No study was identified reporting the incidence of depression (amongst patients with no history of depression) for both minor and major depression in patients with T2DM within the same study. Some studies were identified which reported the incidence for either minor (Luijendijk et al (2008) [45], Aarts (2009)[46]) or major depression (Nefs et al (2012)[11]). Luijendijk et al (2008)[45] report that over five years, 41 out of 2931 people developed minor depression, giving an incidence of minor depression of 1.40% over five years. Aarts (2009) [46] present survival curves for the development of depression after a diagnosis of diabetes. Two curves are presented, one for the development of diagnosed depression and one for the development of diagnosed depression or depressive feelings. Assuming that diagnosed depression relates to major depression and that the combination of diagnosed

depression or depressive feelings relates to major and minor depression, a comparison of the two survival curves suggests an incidence of minor depression of about 3% over 10 years. It was decided to not use either of these studies in the economic model as, based on feedback from clinical experts, the reported incidences were both felt to be unrealistically low.

Of the studies identified, evidence reported by Nefs et al (2012)[11] in the Netherlands was selected for the basecase as this provided data on the incidence of major depression for patients with no depression at baseline and no history of depression. The study followed 2,460 primary care patients with T2DM from 2005 to 2007 (82% of the 2460 were included in the study) treated within 77 primary care practices in South-East Brabant in the Netherlands (median 2.5 years). Depression was defined as a score of ≥12 on the Edinburgh Depression Scale. Imputation was conducted to increase the sample size for analysis. The mean age, percentage of patients with a history of diabetes greater than 3 years, and the proportion of patients with a history of depression was 67±11 years, 61% and 11% respectively. The authors reported that participants who were not depressed at baseline but did have a self-reported history of depression were significantly more likely to experience an incidence of depression during follow-up than those without such a history (33% vs. 13%; $p<0.001$). The percentage of patients who were not depressed at baseline but did have a self-reported history of depression was used in the economic model to estimate the incidence of depression assuming an exponential distribution.

Due to the lack of published evidence, in the basecase the incidence of depression was assumed to be the same for both minor and major depression at 5.4% per year.[11] In reality, it is likely that the incidence for minor depression is higher than the incidence for major depression. A sensitivity analysis was therefore conducted assuming the incidence of minor depression to be double that for major depression. Additional sensitivity analyses were carried out; one halved the incidence of major depression, the other halved the incidence of both minor and major depression.

*Spontaneous recovery (remission) from depression (assuming no treatment)*

Spontaneous recovery rate in the absence of treatment for major depression in individuals with diabetes was taken from Spijker et al (2002).[19] This study estimated the duration of a major depression episode in the general population using the Netherlands Mental Health Survey and Incidence Study (NEMESIS) conducted in an adult population. The diagnosis of

major depression was based on the Composite International Diagnostic Interview (structured interview). Responders were asked whether they had received help for mental problems within the past 24 months in terms of no care, primary care (GP), or mental health system care. The authors reported that the median duration of a major depression episode was 3.0 months and that 76% recovered within 12 months and nearly 20% had not recovered at 24 months. The authors reported that severe depression lengthens the median duration from 3.0 months (95% CI 2.5-3.5) to 7.5 months (95% CI 5.1-10.0). The authors found no differences in time to recovery in the different modalities of care (in those without professional care, those with only primary care and those with mental health system care).. For individuals with major depression (from the general population), a survival curve was presented showing time to recovery in the absence of treatment. This evidence was used in the economic model to estimate the time to spontaneous recovery for major depression assuming a Weibull distribution (with the parameters: alpha = 0.667, beta = 0.673). This distribution has a mean time to spontaneous recovery of 0.877 years.

The time to spontaneous recovery for minor depression was estimated using 11-week response/remission rate reported in NICE CG90 [12] in the general population using an exponential distribution. The authors reported an 11-week response rate of 47.71% and a remission rate of 44.95%. For this project no distinction was made between response and remission. Hence the conservative value of 44.95% was used. This distribution has a mean time to spontaneous recovery of 0.354 years.

*Relapse of depression (following treatment cessation/spontaneous recovery)*

In the economic model, it is assumed that patients with a history of depression (who recovered) are at risk of experiencing a relapse. The risk of relapse for patients with a history of major depression was taken from Lustman et al (2006) for patients receiving placebo. The authors conducted a randomized, double-blind, placebo-controlled, maintenance treatment trial. The study was conducted in the US and included 152 patients with diabetes (T1DM and T2DM) who recovered from major depression during 16 weeks of open-label treatment with sertraline. Patients who recovered from depression were then randomised to either continue to receive sertraline (n=79) or placebo (n=73) and were followed up for up to 52 weeks or until depression recurred. The authors reported that at 1 year, the calculated rate of non-recurrence was 65.8% in patients treated with sertraline compared with 47.9% for those who received placebo. In the economic model the time to relapse was taken from the placebo arm and assumed to follow an exponential distribution,

giving a mean time to relapse of 1.359 years. No studies were identified for minor depression. In the basecase it was assumed that the time to relapse was similar to major depression. Two sensitivity analyses were performed; for one the time to relapse was halved, for the other it was doubled.

### 5.11.2 Current pathway of care for depression in England

Informed by the conceptual modelling process, the review of evidence and NICE guidelines for the management of depression [47], treatment for depression was assumed to use a stepped-care approach to reflect the national treatment pathway for depression.

As previously mentioned, within a stepped-care approach, individuals start with less intensive treatment, and step-up to more intensive treatments if no response is achieved. Clinical advisors indicated that there are regional variations across England on the nature of treatment received at the 1st step. Consequently, different treatment options were considered within each step in the economic model. Whilst it was assumed that all individuals start treatment at step 1 in the economic model, it should be noted that this is not the same as implementing a "pure" stepped care model. For instance, within the model, an individual receiving low-intensity psychotherapy at step 1 and then high-intensity psychotherapy at step 2 may represent an individual being stratified to avoid receiving pharmacotherapy first. Whilst NICE clinical guidance 90 and 91 both recommend a stepped-care approach, the same clinical guidance also suggest that stratification should be made when possible. This was confirmed by clinical advisors.

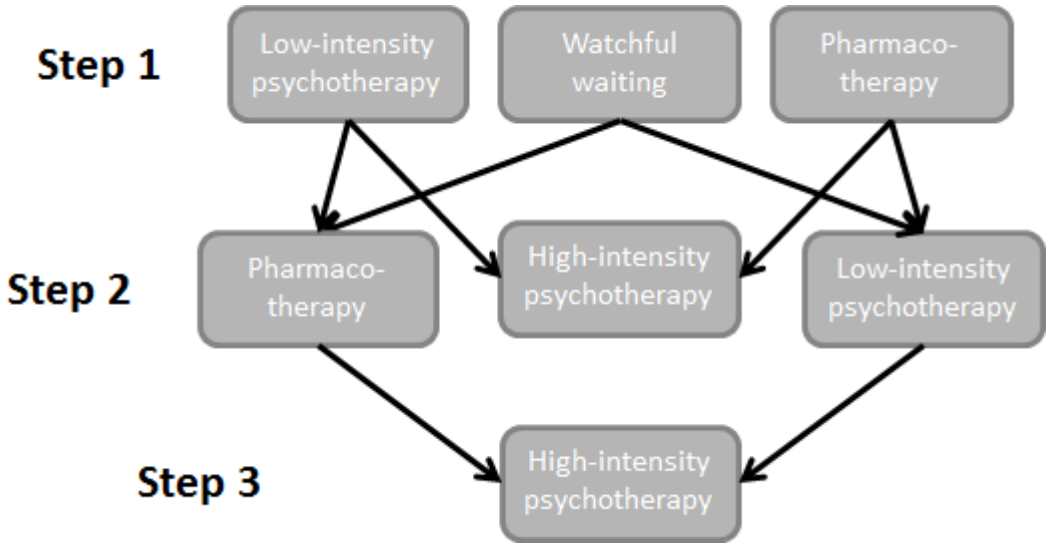
Individuals with T2DM and depression in the economic model could receive any of the following treatments for depression:

- Watchful waiting (or active monitoring): this is based on NICE guidance and constitutes a discussion between the patient and GP about the problem, with information about depression. A follow-up assessment at two weeks is arranged. If the patient has not improved at this follow-up assessment, then patients receive an active treatment.
- Pharmacotherapy: this includes any type of antidepressant medication.
- Low-intensity psychological interventions (psychotherapy): these can take a variety of forms, but can generally be categorised into four groups: structured physical activity, guided self-help based on CBT, peer (self-help) support groups, and computerised CBT.

- High-intensity psychological interventions (psychotherapy): these include: CBT, interpersonal psychotherapy, couple therapy, and counselling.

A schematic of how stepped care treatment for depression is implemented within the economic model is presented in Figure 13.

**Figure 13: Schematic of the depression treatment sub-model**




The following duration of treatment were assumed (Table 17) if treatment was completed

- 2 weeks for watchful-waiting
- 8 weeks for antidepressant therapy based on Tosh et al (2013)[16]
- 22 weeks for low intensity psychotherapy based on Tosh et al (2013)[16]
- 37 weeks for high intensity psychotherapy based on Tosh et al (2013)[16]

The average waiting time for low and high intensity psychotherapy was taken from Richards *et al* (2010).[17] The authors examined the design and implementation of a stepped care model of treatment for common mental health problems across four NHS primary care sites from September 2006 until April 2008. They reported the average waiting times from referral to assessment across all steps and all sites to be 21.8 days (range: 0-224 days).

The waiting time for antidepressant was assumed to be a week. Furthermore, it was assumed that patients who did not respond to antidepressant remain on antidepressants when they step up to low or high intensity psychotherapy.

**Table 17: Duration of treatment and waiting time to start treatment assumed in the economic model**

| | | |
|---|---|---|
| **Duration of treatment (completers)**<br>• Watchful-waiting<br>• Antidepressant<br>• Low intensity psychotherapy<br>• High intensity psychotherapy | <br>2 weeks<br>8 weeks<br>22 weeks<br>37 weeks | <br>Assumption<br>Tosh et al (2013) [16] |
| **Waiting list**<br>• Watchful-waiting<br>• Antidepressant<br>• Low intensity psychotherapy<br>• High intensity psychotherapy | <br>0<br>7 days<br>21.8 days<br>21.8 days | <br>Richards et al (2010) [17]<br>Assumption |

Finally, patients at step 3, who do not response to treatment, are assumed to remain on treatment at step 3 for a maximum duration of 3 years.

The following parameters were required for the economic model:

- Distribution of treatment received at step 1 in England across the 3 treatment options in Figure 14
- Distribution of treatment received at step 2 (given treatment received in first line) in England

*Evidence on the distribution of treatment received at step 1 in England*

No study was identified describing the distribution of treatment received at the first step in England. A study were identified on the distribution of treatment received (irrespective of the step) in the general population but not considered further as this did not provide information for the distribution of treatment received at the first step [17]. Similarly, some studies were identified which described the distribution of treatment received in the first step in other European countries, but it was felt inappropriate to use evidence from other countries due to differences in care.

Consequently, due to the lack of evidence on the distribution of depression treatment received at first step in patients with T2DM in England, an assumption was used and was varied in sensitivity analysis. It was assumed that 90% of patients with minor depression receive watchful waiting at the first step, with the remaining 10% separated equally between pharmacotherapy and low intensity psychotherapy. For patients with major depression, it was assumed that 10% would receive watchful waiting, with the remainder split between pharmacotherapy (70%) and low intensity psychotherapy (20%) (Table 18). In

a sensitivity analyses it was assumed that everyone with major depression received antidepressant treatment as a first line treatment.

**Table 18: Distribution of treatments at step 1 assumed in the economic model**

| Depression type | Pharmacotherapy | Low-intensity psychotherapy | Watchful waiting |
|---|---|---|---|
| Minor | 5% | 5% | 90% |
| Major | 70% | 20% | 10% |

*Evidence on the distribution of treatment received following treatment received at step 1*

Similarly, there is limited evidence on the distribution of treatment received following treatment received at step 1. Tosh et al, 2013 [16] reported the distribution of second line treatments conditional upon patients receiving pharmacotherapy in first line in the general population with major depression. The authors reported that, of people who stepped-up from pharmacotherapy, 68% received low-intensity psychotherapy and 32% received high-intensity.

No evidence was identified for the distribution of treatment received following watchful waiting or low-intensity psychotherapy and the following assumptions were used (Table 19):

- Individuals receiving watchful-waiting, moved to low-intensity psychotherapy (30%) or pharmacotherapy (70%) irrespective of severity of depression, if they did not spontaneously recover.
- 100% of patients with minor depression who did not respond to pharmacotherapy would be stepped up to low-intensity psychotherapy
- 68% and 32% of patients with major depression who did not respond to pharmacotherapy would move to low intensity and high intensity psychotherapy respectively
- 100% of patients who did not respond to low-intensity psychotherapy would be stepped-up to high-intensity psychotherapy.

A sensitivity analyses was performed which assumed that following watchful waiting, individuals who stepped up would all receive antidepressants.

**Table 19: Distribution of treatments at step 2 assumed in the economic model**

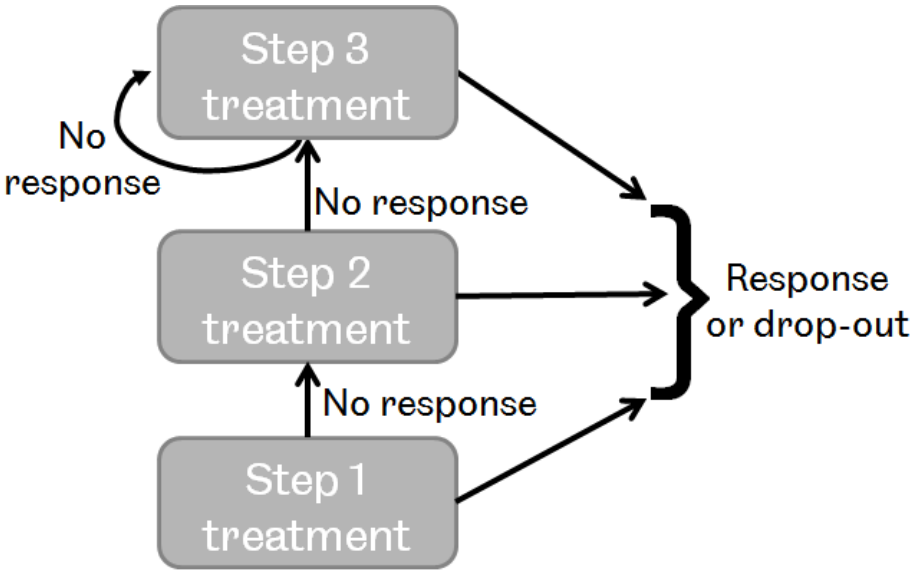
| Depression type | Pharmacotherapy | Low-intensity psychotherapy | High-intensity psychotherapy |
|---|---|---|---|
| **Following watchful waiting** | | | |
| Minor | 70% | 30% | 0% |
| Major | 70% | 30% | 0% |
| **Following pharmacotherapy** | | | |
| Minor | 0% | 100% | 0% |
| Major | 0% | 68% | 32% |
| **Following low-intensity psychotherapy** | | | |
| Minor | 0% | 0% | 100% |
| Major | 0% | 0% | 100% |

### 5.11.3 Treatment effect on depression natural history

In the economic model individuals are assumed to be treated for a pre-defined duration (2 weeks for watchful-waiting, 8 weeks for antidepressant, 22 weeks for low intensity psychotherapy and 37 weeks for high intensity psychotherapy).

Individuals in the model can either complete their course of treatment (for which they may either respond to treatment or not) or drop out from treatment before the end of the treatment course. This is described in Figure 14. It should be noted that successful treatment may not result in a shorter time to recovery. If an individual was due to spontaneously recover from their depression during their treatment, then successful treatment will not have affected the amount of time spent with depression. This is depicted in Appendix 12.

**Figure 14: Effect of treatment**



The probability of drop-out is evaluated at the start of each course of depression treatment. If an individual drops-out, they are assumed to not respond to treatment, and they leave the depression treatment sub-model half-way through treatment. Drop-out varies depending on whether the patient has minor or major depression (no distinction is made within the major depression category) or treatment received.

If an individual does not drop-out of treatment (therefore complete the treatment course), they have a probability of responding to treatment. If the individual does not drop-out and they do not respond to treatment then they remain in the depression treatment sub-model, moving up a step until they reach step 3. Individuals at step 3 remain there until they either respond to treatment, drop out, experience spontaneous recovery or their length of treatment exceeds three years. If treatment for a single episode of depression exceeds three years it was assumed that treatment for that episode of depression is stopped, as it was felt that individuals would not remain on treatment for longer than this time period. The probability of response was assumed to vary depending on the individual's severity of depression (minor vs. major - no distinction is made within the major depression category) and treatment received. Non-responders to treatment are assumed to receive the full treatment duration unless they spontaneously recover.

Finally, if individual does not drop out and respond to treatment, it is assumed that patients complete the course of treatment (unless spontaneous recovery is earlier than the end of treatment) and leave the depression treatment sub-model at the end of treatment. Their depression status is updated to having normal mood (no depression), with a history of past depression. The probability of response was assumed to vary depending on the individual's severity of depression (minor vs. major) and treatment received.

Response is not considered for patients receiving watchful waiting as this was not considered as an active treatment. Patients can either drop out, or recover spontaneously and revert to the 'non-depressed' health state. If patients do not drop out, and do not spontaneously recover, they step-up to active treatment.

Parameters used in the economic model are summarised in Table 20:

**Table 20: Treatment effectiveness data used within the economic model**

| | Minor depression | Major depression | Source |
|---|---|---|---|
| Probability of remission under no treatment | 20% | | NICE CG91 [18] |
| Effect size for response compared to no treatment:<br>Pharmacotherapy<br>Low-intensity psychotherapy | RR= 1.01<br>RR= 1.16 | OR= 2.50<br>OR= 2.88 | NICE CG90 [18] for minor<br>Baumeister (2012) [19] for major |
| Probability of responding to pharmacotherapy | 20.18% | 38.46% | Derived from above |
| Probability of responding to low-intensity psychotherapy | 22.81% | 41.86% | Derived from above |
| Effect size for response for high-intensity compared to low-intensity psychotherapy | RR= 2.25 | | Tosh *et al* (2013) [16] |
| Probability of responding to high-intensity psychotherapy | 44.14% | 61.83% | Derived from above |
| Probability of dropping-out<br>Pharmacotherapy<br>Low-intensity psychotherapy<br>High- intensity psychotherapy<br>Watchful waiting | <br>31.55%<br>30.00%<br>30.00%<br>10% | <br>31.55%<br>30.00%<br>30.00%<br>35% | NICE CG90 [18]<br>Baumeister (2012) [19]<br>Assumption<br>Assumption |

RR: Relative Risk; OR: Odds Ratio

*Evidence on response to treatment*

The scoping search of reviews identified two systematic reviews that reported synthesised treatment effects for both pharmacological and psychological treatments for major depression amongst people with diabetes. One review was by Van Der Feltz-Cornelius *et al* (2010) [48], the other was a Cochrane review (Baumeister et al., 2012[19]). Evidence from the Baumeister review [19] was preferred as this included more recent studies; outcome measures on depression remission, and could be used directly in the economic model. Further details on this study are available in section 2.2. Using meta-analysis, the study reported an OR for remission of 2.50 for pharmacological treatment compared with no treatment and 2.88 for psychological treatment compared with no treatment.

Response rates for each treatment were calculated by applying published effect sizes to the probability of spontaneously responding (recovering) in the absence of treatment. NICE clinical guidance on depression with a chronic physical health problem [18]uses a

spontaneous recovery rate of 20% for individuals with major depression. This value was based on the expert opinion on the guideline development group.

None of these reviews reported the effectiveness for high-intensity psychotherapy for major depression amongst people with diabetes. The effect size for low-intensity psychotherapy was adjusted using the relative effectiveness between high and low-intensity psychotherapy (RR = 2.25) reported by Tosh et al (2013) [16]. The treatment effectiveness data used in this study was based on local IAPT data.

No study was identified which provided evidence on the effectiveness of treatments for individuals with minor depression and diabetes. Instead, due to the lack of identified evidence, evidence from the general population reported in the NICE CG90 [13] for pharmacological and psychological intervention was used. The study reported a RR of 1.01 for pharmacological treatment compared with no treatment and a RR of 1.16 for psychological treatment compared with no treatment.

As for major depression, the effect size for low-intensity psychotherapy for minor depression was adjusted using the relative effectiveness between high and low-intensity psychotherapy (RR=2.25) reported by Tosh et al (2013) [16].

*Evidence on drop out*

No robust evidence was identified on the probability of dropping out from treatment for individuals with major depression and T2DM. In addition, No study was identified which provided evidence on the drop-out rates for individuals with minor depression and diabetes. Instead, due to the lack of identified evidence, evidence from the general population reported in the NICE clinical guidance 90 [12] for pharmacological and psychological intervention was used. For pharmacological interventions, 55 individuals out of 187 dropped-out, giving a drop-out rate of 31.55%. Hence the drop-out rate for minor depression for pharmacotherapy (31.55%) was used for both minor and major depression in the model. It was further assumed that the drop-out rate for low-intesnity psychotherapy would be 30% for both minor and major depression.

No studies reported drop-out rates from high-intensity psychotherapy for either major or minor depression amongst people with diabetes. Hence it was assumed that this drop-out rate would be the same as from low-intensity psychotherapy (30%).

For watchful-waiting, patients were able to drop-out if they did not return for assessment at two weeks. No evidence was identified during our rapid searches. A 10% and 35% drop out rate for patients with minor and major depression respectively were assumed.

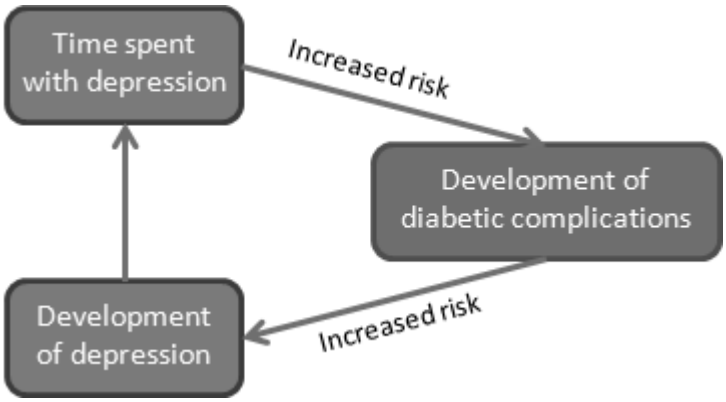
The probability of dropping-out was varied in sensitivity analyses; for one the probability was set to 15% for all treatments and for the other it was set to 45%.

### 5.12 Bi-directional relationship between depression and diabetes-related complications

Following the evidence review, and discussion with advisors, the relationship between depression and diabetes was modelled assuming a direct link through complications (Figure 15) where:

- Depressed individuals have a higher risk of developing diabetes-related complications
- Individuals with diabetes-related complications have a higher risk of developing depression.

**Figure 15: Relationship between developing a diabetes-related complication and developing depression**




Non-depressed individuals have an annual probability of developing a diabetes-related complication based on the UKPDS risk equations [6]. It was assumed that the risk equations and diabetes-related risk factors for complications from the UKPDS were for non-depressed individuals. This is a limitation as some patients may have had depression.

If an individual has depression (diagnosed or not, treated or not), the risk of developing diabetes-related complications is elevated (compared with non-depressed individuals) in the

model. As diabetes-related complications are assessed on an annual basis, the amount of time spent with depression in the preceding year is used to weight this risk (for example, if an individual spent half of the year with depression, then the risk is halved). Further, if an individual with depression is receiving depression treatment, and if they will respond to their depression treatment (this is evaluated at the start of each step of treatment), their time spent with depression does not contribute towards the elevated risk.

On the other hand, if an individual has a diabetes-related complication, the time to developing depression is shortened. Data used in the economic model for the effect of depression on diabetes-related complications and the effect of diabetes-related complication and development of depression are summarised in Table 21. These are separated by micro (IHD, Blindness, Renal failure) and macrovascular diabetes-related complications (CHF, MI, Stroke, Diabetes ulcer, Amputation) and by minor and major depression.

**Table 21: Bi-directional links between depression and diabetes included within the economic model**

| Progression | Minor depression | Major depression | Source |
|---|---|---|---|
| Hazard ratio for developing a microvascular diabetes-related complication due to having depression | 1.31 | 1.36 | Lin et al (2010) [2] |
| Hazard ratio for developing a macrovascular diabetes-related complication due to having depression | 1.0 | 1.25 | Lin et al (2010) [2] |
| Hazard ratio for developing depression due to having a microvascular diabetes-related complication | 1.5 | 1.5 | Assumption |
| Hazard ratio for developing depression due to having a macrovascular diabetes-related complication | 1.5 | 1.5 | Assumption |

The risk of developing depression conditional on the presence of diabetes-related complications was applied to both incidence (amongst individual with no history of depression) and relapse of depression (amongst individual with a history but no current depression). Of note, the presence of diabetes-related complications was only assumed to affect the incidence and of depression, and this risk was assumed to only apply for the year

in which the complication developed as it was assumed that the risk was on diagnosis, and decreased over time as patients adjusted to their current health status. Furthermore, it was assumed that the risk of developing depression was the same if individuals had one or several complications.

A systematic review of the relationship between depression and diabetes-related complications was carried out to identify evidence that could be used to inform this relationship. Details of this review are provided in section 2.4. Preference was given to studies that reported outcomes for both micro and macrovascular complications, by severity of depression (minor, major) and longitudinal studies (as cross-sectional studies cannot attribute causality).

*Risk of developing diabetes-related complications according to depression status*

Three studies were identified which looked at the impact of depression on diabetes-related complications. The key characteristics of each study are described in section 2.4. Black et al (2003) [49] did not report the HR for major depression. Furthermore, Black et al (2003) was conducted in older patients with T2DM in Mexico, limiting the generalizability of results; whilst Lin et al (2010) [2] and Sullivan et al (2012) [50] reported results from a study in the US/Canada. Results from the Lin study [2] was used in the basecase (Table 21) as the results from Sullivan et al (2012) [155] lacked face validity (they report a hazard ratio below one for the link between major depression and developing microvascular complications, implying that individuals with major depression were less likely to develop microvascular complications than indviduals without major depression). These values were varied in sensitivity analyses; for one analysis no elevated risk of diabetes complications due to having depression was assumed, for another HRs of 1.5 were used throughout and for another HRs of 2 were used.

It was also assumed that patients with depression were more likely to develop hypoglycaemia (section 5.8.2) based on Katon et al(2013) [7].

*Risk of developing depression according to the presence of diabetes-related complications*

No study was identified that examined the impact of having diabetes-related complications on the development of depression. Cross-sectional studies were identified, but it is unclear whether depression caused diabetes-related complications or the opposite. In the absence of evidence, it was assumed that patients with diabetes-related complications had a 50%

increased risk of developing depression compared with patients with no diabetes-related complication. This value was varied in sensitivity analyses. One analysis assumed no increased risk, another assumed that risk was tripled, another assumed that the 50% increase was only observed for microvascular complications and another analysis assumed that the 50% increase was only observed for macrovascular complications.

**5.13 Measurement and valuation of health effects**

Preference based utility data were used to calculate quality adjusted life years (QALY) and the EQ-5D data was sourced where possible as this is the instrument preferred by NICE [5]. The baseline utility weights for patients with diabetes and the decrements in health related quality of life (HRQoL) associated with MI, IHD, stroke, heart failure, amputation and blindness was taken from the most recent analysis of the UKPDS (Alva et al, 2013) [21]. The authors analysed longitudinal data (between 1997 and 2007, including seven questionnaires) from the UKPDS to estimate HRQoL decrements with EQ-5D associated with six diabetes-related complications. The authors reported that about 3,380 patients completed at least one EQ-5D questionnaire, with a mean of 3.4 questionnaires completed per patient providing a total of 11,614 responses for the analysis. The authors constructed statistical linear regression models (ordinary least square (OLS) and Fixed effect (FE) estimator) including different interaction and/or covariates. The recommended FE regression model was used in the current analyses. As different coefficients are presented for age (for the 7 survey round) the average value was used (-0.144).

For consistency with the method used to apply the Alva data, all utility values for the other health states were applied as constant absolute decrements. The decrement in utility associated with foot ulcer was taken from Solli et al (2010) [23]. The study was conducted in Norway and included 521 respondents, of which 356 had T2DM. HRQoL was assessed using EQ-5D derived using the UK TTO tariff. The authors estimated the decrement in utility associated with foot ulcer to be -0.083 (-0.271 to 0.105) in T1DM and -0.016 (-0.134 to 0.101) in T2DM using OLS regressions. For comparison, the additional Solli et al decrements were broadly comparable to the estimate from the UKPDS[21] in England for stroke (-0.135 vs. -0.165) and IHD (-0.037 vs. -0.028).

The decrement in utility associated with severe hypoglycaemia was taken from a US study by Marrett et al (2011)[24] in patients with T2DM treated with oral antihyperglycemic agents from the US National Health and Wellness Survey 2007. Hypoglycaemic episodes were

classified by severity defined as mild (no interruption of activities), moderate (some interruption of activities), severe (needed assistance of others), or very severe (needed medical attention). HRQoL was assessed using EQ-5D. The authors reported the utility decrement to be 0.045, but varied by level of severity (0.009 for mild, 0.055 for moderate, 0.131 for severe and 0.208 very severe episodes). In the economic model, the average utility decrement associated with severe and very severe hypoglycaemic episodes was used (0.1695). It was also assumed that a severe hypoglycaemic episode lasts 4 days based on the Warren et al (2004).[51] Therefore, in the model, a severe hypoglycaemic event was assumed to be associated with a utility detriment of 0.00186 (decrement of 0.1695 for 4 days).

The decrement in utility for individuals with renal failure was taken from an economic evaluation conducted in Canada for antihyperglycemic therapy in patients with type 2 diabetes mellitus inadequately controlled on metformin [22]. The authors reported a decrement of -0.263 for the first and subsequent years. It is unclear from the publication whether the EQ-5D was calculated using the UK or US tariff, or whether it applied to individuals on dialysis or receiving a transplant.

Evidence on the impact of depression on QoL for patients with diabetes is more scarce. No studies were identified in patients with diabetes and depression hence an estimate was taken from the general population (Kaltenthaler et al, 2006).[52] EQ-5D data collected in the PHASE RCT of supervised self-help CBT in primary care was analysed. The study included 62 patients recruited from 17 primary healthcare teams. The authors calculated the mean (SD) EQ-5D scores for three depression categories of mild to moderate, moderate to severe and severe, to be 0.78 (0.20), 0.58 (0.31) and 0.38 (0.32), respectively. The authors also reported that the age and gender-matched normal scores for this group was 0.88 (0.22). Using this information, the absolute average decrement in utility was estimated to be -0.1 for patients with mild depression, -0.3 for patients with moderate depression, and -0.5 for patients with severe depression. For the basecase analysis, the decrement for moderate depression (-0.3) was assumed to apply for major depression. Decrements for mild depression (-0.1) and severe depression (-0.5) were used in sensitivity analyses. For comparison, a recently published study using data (N=11080) from the Adult Psychiatric Morbidity Survey (APMS) which was designed to provide information on the prevalence of psychiatric conditions for people living in Great Britain [53]. The most common mental health disorder was found to be Mixed Anxiety Depressive Disorder (10%). The mean EQ-5D for the full sample was 0.808

(sd 0.206), this increased to 0.851 in respondents who had no physical health problem (N=5879), and to 0.842 in respondents with no mental health problems (N=8263). The mean EQ-5D was reported to be 0.513 in respondents with long term depression (N=187) and 0.537 in depression sufferers (N=367).

Given the model structure and simplified assumption about the impact of treatment, adjustment was made for individuals on treatment responding to therapies. It was assumed that the utility decrement whilst on treatment was -0.15 for major depression if the individual will respond to treatment to account for the fact that whilst on successful treatment depression is improving. No decrement in utility was assumed for patients with minor depression as per Kaltenthaler et al (2006) [25]. A summary of the quality of life data used within the economic model is presented in Table 22.

**Table 22: Utility weights used within the economic model**

| Health state | Decrement | Reference |
|---|---|---|
| Baseline | 0.807 | Alva et al (2013) [21] |
| Decrement for age | -0.144 | Alva et al (2013) [21] |
| MI (year before) | -0.065 | Alva et al (2013) [21] |
| MI (prior history) | 0.008 | Alva et al (2013) [21] |
| IHD | -0.028 | Alva et al (2013) [21] |
| Stroke | -0.165 | Alva et al (2013) [21] |
| Heart Failure | -0.101 | Alva et al (2013) [21] |
| Amputation | -0.172 | Alva et al (2013) [21] |
| Blindness | 0.033 | Alva et al (2013) [21] |
| Renal failure | -0.2630 | Klarenbach et al (2011) [22] |
| Foot ulcer | -0.016 | Solli et al (2010) [23] |
| Hypoglycaemia | -0.00186 | Marrett et al (2011) [24] and Solli et al (2010) [23] |
| Minor depression | 0 | Kaltenthaler et al (2006) [25] |
| Major depression | -0.3 | Derived (Kaltenthaler et al (2006)) [25] |
| Effect of being on depression treatment on the decrement for major depression; responders only (multiplier) | x0.5 | Assumption |

A constraint is added so that the estimated utility weights remain within the bounds of the EQ-5D (-0.596 to 1).

### 5.14 Resource use and unit costs

#### 5.14.1 Resource use

Resource use (other than resource use associated with the management of diabetes related complications) used in the model are summarised in Table 23. Resource use associated with the management of diabetes-related complications is included separately within the management costs of the complication.

**Table 23: Summary of resource used in the economic model**

| Elements | Resource use | Reference |
|---|---|---|
| Annual review | 1 primary care appointment | Assumption |
| Structured interview | 1 primary care appointment | Assumption |
| Number of primary care appointments for patients with diabetes and no depression | 12.5 | Bhattarai et al (2013) [9] |
| Number of primary care appointments for patients with diabetes and depression (other than treatment for depression) | 8 | Assumption |
| Number of primary care appointment for patients on antidepressant (initial treatment) | 3 if complete (responder/non-responder)<br>1 if drop out | Tosh et al (2013) [16] and assumption |
| Number of primary care appointment for patients receiving watchful-waiting (completers) | 2 if complete (responder/non-responder)<br>1 if drop-out | Assumption |
| Number of low intensity psychotherapy session for completers responder/non-responder) | 3 IAPT +1 assessment<br>2 primary care appointments | Tosh et al (2013) [16] and assumption |
| Number of low intensity psychotherapy session if drop out | 1 IAPT +1 assessment<br>1 primary care appointment | Tosh et al (2013) [16] and assumption |
| Number of high intensity psychotherapy session for completers responder/non-responder) | 7 IAPT +1 assessment<br>2 primary care appointments | Tosh et al (2013) [16] and assumption |
| Number of high intensity psychotherapy session if drop out | 3 IAPT +1 assessment<br>1 primary care appointment | Tosh et al (2013) [16] and assumption |

*Annual review*

The annual review was assumed to incur one primary care appointment.

*Structured interview*

The structured interview was assumed to incur one primary care appointment (lasting less than 17.2 minutes).

*Ongoing management of diabetes/other than management of depression)*

It was assumed that on average, non-depressed individuals with T2DM had 12.5 primary care appointment per year based on Bhattarai et al (2013).[42] Depressed individuals with T2DM were assumed to attend 8 primary care appointments per year as opposed to 12.5 (section 5.9).

*Watchful waiting*

It was assumed that completers to watchful waiting had 2 primary care appointments (one at the beginning and one at the end of 2 weeks), whilst patients who drop out only incur one primary care appointment.

*Treatment with antidepressant*

The length of antidepressant treatment was based on Tosh et al (2013)[16], and was assumed to be 8 weeks if an individual completes the treatment course or 4 weeks if they drop out from treatment. Assuming a primary care visit at the start of treatment, a primary care visit every month and one primary care visit at the end of 8 weeks, it was assumed that completers (responder and non-responders) incur 3 primary care appointments; whilst patients who drop out only incur 1 primary care appointment.

*Low and high-intensity psychotherapy*

It is assumed that psychotherapy is given through IAPT services. This is a simplification as in reality IAPT may not be available to everyone in England. Based on Tosh et al (2013)[16] it was assumed that responders to low-intensity IAPT incur 4 IAPT appointments (3+1 assessment) whilst patients dropping out from low-intensity IAPT incur 2 IAPT appointments (1+1 assessment). Patients on low-intensity IAPT are also assumed to have 2 primary care appointments if responding to treatment or 1 primary care appointment if they drop out of treatment.

Similarly, based on Tosh et al (2013)[16] it was assumed that responders to high-intensity IAPT incur 8 IAPT appointments (7+1 assessment) whilst patients dropping out from IAPT incur 4 IAPT appointment (3+1 assessment). Patients on low-intensity IAPT are also assumed to have 2 primary care appointments if they respond or 1 primary care appointment if they drop out of treatment.

### 5.14.2 Unit costs

Unit costs are summarised in Table 24.

**Table 24: Unit costs used in the economic model**

| Unit costs | Value (£) | Reference |
|---|---|---|
| Annual review | £397 | NAO [26] |
| GP appointment (lasting 11.7 minutes) | £37 | PSSRU [27] |
| GP appointment (lasting 17.2 minutes) | £55 | PSSRU [27] |
| Screening for depression | £2 | Assumption |
| Antidepressants (daily costs) | £0.072857 | Tosh et al (2013) [16] |
| IAPT | £88 | Tosh et al (2013) [16] |
| Cost of depression treatment | | |
| Antidepressant treatment (completers) | £115.08 | Based on resource use and unit costs |
| Antidepressant treatment (drop out) | £57.54 | Based on resource use and unit costs |
| Low intensity psychotherapy (completers) | £426 | Based on resource use and unit costs |
| Low intensity psychotherapy (drop out) | £213 | Based on resource use and unit costs |
| High intensity psychotherapy (completers) | £778 | Based on resource use and unit costs |
| High intensity psychotherapy (drop out) | £389 | Based on resource use and unit costs |
| Diabetes-related complications | | |
| Diabetes – no complications | £252[a] | Clarke et al (2003) [28] |
| CHF – year of event | £3,559[a] | Clarke et al (2003) [28] |
| IHD – year of event | £3,139[a] | Clarke et al (2003) [28] |
| MI – year of event | £6,522[a] | Clarke et al (2003) [28] |
| Stroke – year of event | £3,793[a] | Clarke et al (2003) [28] |
| Blindness – year of event | £1,397[a] | Clarke et al (2003) [28] |
| Ulcer – year of event | £1,855[a] | Ghatnekar et al (2002) [29] |
| Amputation – year of event | £13,556[a] | Clarke et al (2003) [28] |
| Renal failure – year of event | £34,806[a] | NICE STA for dapagliflozin [30] |
| CHF – subsequent years | £1,011[a] | Clarke et al (2003) [28] |
| IHD – subsequent years | £790[a] | Clarke et al (2003) [28] |
| MI – subsequent years | £744[a] | Clarke et al (2003) [28] |
| Stroke – subsequent years | £399[a] | Clarke et al (2003) [28] |
| Blindness – subsequent years | £450[a] | Clarke et al (2003) [28] |
| Ulcer – subsequent years | £21[a] | Ghatnekar et al (2002) [29] |
| Amputation – subsequent years | £481[a] | Clarke et al (2003) [28] |
| Renal failure – subsequent years | £34,806 | NICE STA for dapagliflozin [30] |
| Severe hypoglycaemia | £390 | NICE STA for dapagliflozin [30] |

[a]uplifted to 2013 [54;55]

*Cost associated with the annual review*

Data on the cost of the annual review are limited. The 2012 report published by National Audit Office (NAO) reported an NHS spending of £840 million for the annual reviews in primary care [56]. However, it is unclear from the report what this estimate includes or excludes. The same source reports that 2.34 million people aged 16 years and older were diagnosed with diabetes in England in 2009-2010. Assuming that 90.4% of patients with diabetes attend the annual review (section 5.9.1), the cost associated with the annual review was estimated to be £397.

*Primary care unit costs*

The cost associated with a Primary care appointment was taken from the Personal Social Services Research Unit (PSSRU) 2013 and was assumed to be £37 for appointments lasting less than 11.7 minutes and £55 for appointments lasting less than 17.2 minutes.

*Cost associated with screening*

In the basecase, it was assumed that screening using the Whooley questions lasts 2 minutes, for an additional cost of £2. Two sensitivity analyses were conducted to assess the effect on results when assuming costs of £4 and £0 for screening.

*Cost of antidepressant*

The daily cost of antidepressant was assumed to be £0. 073 [16].

*Cost associated with IAPT*

The cost associated with the use of IAPT service was taken from Tosh et al (2013) [16] and was assumed to be £88 per session. The cost was assumed to be same for both low and high intensity IAPT. It was assumed that the personnel delivering low and high IAPT would be the same, but that the activities delivered would be different, as would the number of sessions. The total cost of low-intensity psychotherapy as used in the economic model was £436, whilst for high-intensity psychotherapy it was £778.

*Cost associated with the management of diabetes-related complications*

The costs associated with the management of CHF, IHD, MI, stroke, amputation and blindness in the UK were taken from Clarke et al (2003)[28] and inflated to 2013 (Table 24).[54;55] The management cost for these complications was assumed to be different in the first year of the event and subsequent years. The cost associated with the management

of foot ulcer was taken from Ghatnekar et al (2002)[29], as reported in a previous single technology appraisal (STA) for dapagliflozin [30], and uplifted to 2013.[54;55] The cost was assumed to be different for the first year of the event and subsequent years. The cost associated with the management of renal failure was taken from the cost used in a previous STA for dapagliflozin [30]. The cost was assumed to be different the first year of the event and subsequent years. Finally, the cost associated with an episode of severe hypoglycaemia was assumed to be £390 based on the cost reported in the STA for dapagliflozin [30].

**5.15 Estimating the societal impact**

A wider societal perspective was also explored, considering the impact on productivity (in terms of days off work due to ill-health) and informal care (days received any unpaid care provided by family or friends). The methodology used was taken from publications describing research conducted to inform the DH's proposed approach to Value Based Pricing. Reports and full details of these work are available online [31;32].

A regression model (two step approach) was used to estimate the average number of days off work (in the last 6 weeks) due to ill health based on age, gender, EQ-5D index score and primary ICD-10 diagnosis. The regression parameter coefficients used, and a worked example is presented in Appendix 14.

Similarly, a regression model was used to estimate the average number of days in the last six weeks requiring informal care (at any point during the day) based on an individual's age, gender, EQ-5D index score, and their primary ICD-10 diagnosis. The estimation process used a zero-inflated negative binomial regression model with variable inflation.

For use within this project, each individual's primary ICD-10 diagnosis was set to 'Diabetes', and the impact of any diabetes complications (including depression) was captured via changes in the EQ-5D index score.

**5.16 Policy questions addressed**

Informed by discussions with the advisory group and service users, the following changes to the depression pathway were considered.

More frequent opportunistic screening

Opportunistic screening refers to screening for depression that is not planned in advance, but occurs on an ad-hoc basis during any primary care appointment. A potential change is to improve the proportion of primary care appointments that include an opportunistic depression screen. Under current practice, it was assumed that each primary care appointment has a 20% probability of including an opportunistic screen for patients with undiagnosed depression or 5% probability for patients with no current depression. The effect of assuming that every primary care appointment included an opportunistic screen was assessed. This policy should identify more episodes of depression.

Implementing collaborative care for depression treatment

Collaborative care is an enhancement to how depression treatment is usually delivered. It requires an additional healthcare professional, whose job is to improve collaboration between the individual receiving depression treatment and those delivering the depression treatment [57]. It has been trialled amongst individuals with depression amongst the general population in the United Kingdom [58], and has been trialled in the United States as a treatment enhancement for individuals with diabetes and comorbid depression [59]. Although collaborative care is recommended by NICE clinical guidelines for individuals with depression and a long-term chronic physical health problem [18], it is not yet routinely implemented within the United Kingdom, although there is an on-going trial for individuals with depression and diabetes and/or coronary heart disease. [60]

The additional resource use associated with collaborative care (i.e. in addition to current resource use associated with the management of depression) were based on resource use patterns described in NICE CG91 [10]. The effectiveness of collaborative care was taken from a recently published meta-analysis by Huang et al (2013) [20]. The analysis included eight studies containing 2,238 patients. The authors reported that collaborative care was associated with a significant improvement in depression treatment response (RR =1.33, 95% CI =1.05-1.68), depression remission (adjusted RR =1.53, 95% CI =1.11-2.12) and higher rates of adherence to antidepressant medication (RR = 1.79, 95% CI =1.19-2.69). In the economic

model, it was assumed that the RR for response and non-drop-out rate for patients with CC was 1.33 and 1.79 respectively compared with UC.

In NICE CG91 it was assumed that the case manager in the collaborative approach co-ordinates care and is in face to face contact or telephone contact with the service use 10 times over the 6 month period of treatment and has three contacts over the 6 months maintenance period. It was also assumed that the case manager liaises with the GP and that the case manager will undergo supervision by a senior mental health professional. An average of 8 minutes for contact over 3 months for liaison with the GP at a cost of £0.47 per minute was assumed. Furthermore, 2 minutes supervision time per patient was assumed for a 30 to 35 patient caseload at a cost of £0.47 per minute.

Based on these estimates, the number of telephone contacts, face to face contacts, liaison time with GP and supervision time and costs assumed in the economic model are summarised in Table 25, for patients on antidepressants, low psychotherapy and high psychotherapy, for completers (responders/non-responders). Individuals dropping out of treatment were assumed to incur half the cost. Unit costs were taken from the NICE CG91[18]. A cost of £33 per hour of client contact was assumed for face to face contact, £28 for telephonic contact. The cost associated with liaison with GP and supervision by a psychiatrist was assumed to be £0.47 and £0.47 respectively.

**Table 25: Estimated resource use and costs associated with the addition of a case manager**

| | Telephone contact | Face to face contact (1 hour) | Face to face contact (30 minutes) | Liaison with GP (minutes) | Supervision by a psychiatrist (minutes) | Total cost |
|---|---|---|---|---|---|---|
| Antidepressant | | | | | | |
| Completers | 3 | 1 | 1 | 8 | 8 | £85 |
| Drop-out | | | | | | £43 |
| Low psychotherapy | | | | | | |
| Completers | 8 | 1 | 1 | 16 | 22 | £142 |
| Drop-out | | | | | | £71 |
| High psychotherapy | | | | | | |
| Completers | 12 | 2 | 2 | 24 | 37 | £240 |
| Drop-out | | | | | | £120 |

The role of case manager does not currently exist within England, so the costing used in the NICE CG91 economic model [18] is based on assumptions and was varied in sensitivity analyses.

**5.17 Sensitivity analyses**

Due to computational restrictions, no probabilistic sensitivity analysis (PSA) was conducted. A number of univariate sensitivity analyses were conducted on key model parameters to determine if the model results were robust to variations in the values used. The following parameters were varied.

In the basecase, it was assumed that 5% (15%) of GP appointments included a screen for patients with no history of depression (patients with a history of depression). These values were varied in sensitivity analysis assuming that the rates were doubled and halved.

Due to the lack of published evidence, the incidence of depression was assumed to be the same for minor and major depression in the basecase. In reality, it is likely that the incidence for minor depression is higher than the incidence for major depression. A sensitivity analysis was conducted assuming the incidence of minor depression to be double that for major depression. Two further sensitivity analyses were conducted; one which halved the incidence of major depression and one which halved the incidence of both types of depression.

It was believed that individuals with diabetes and depression are less likely to attend primary care appointments than individuals with diabetes alone (excluding appointments associated with their depression treatment). Consequently, in the basecase, it was assumed that individuals with minor and major depression had 8 primary care appointments a year (other than those associated with their management of depression). I.e. a reduction of around 35% of attending primary care appointments compared with non-depressed individuals. A sensitivity analysis was conducted assuming the same number of primary care appointments as for non-depressed individuals. A further sensitivity analysis assumed that individuals with depression had 4 primary care appointments a year.

There were also uncertainty on the link between diabetes related complications and depression, and the link between depression and diabetes related complications. In the basecase, a 50% increase (RR: 1.5) in the risk of developing depression was assumed if an individual experienced a diabetes related complication. This value was varied in sensitivity analysis assuming the risk of developing depression was tripled (RR: 3), was not present (RR: 1), was only present for microvascular complications and was only present for macrovascular complications. The link in the other direction (depression increasing the probability of a

diabetes complication) was also varied; one sensitivity analysis assumed no link (RR = 1), another assumed a RR of 1.5 for major and minor, and another assumed a RR of 2 for major and minor.

In the basecase it was assumed that opportunistic screening occurred at an additional cost of £2. Two sensitivity analyses were conducted, one assuming a cost of £4 for screening the other no cost.

There was also uncertainty on the impact of depression on quality of life. In the basecase the absolute decrements in utility used was -0.3 for major depression. Two sensitivity analyses were conducted, one using an absolute decrement of -0.1 for major depression, the other using a decrement of -0.5 for major depression.

The baseline prevalence of depression and the time to relapse were also varied in sensitivity analyses by doubling and halving their basecase values.

Four sensitivity analyses were conducted regarding depression treatment. In one sensitivity analysis, all individuals with major depression received antidepressant medication as first-line treatment. In another analysis, all individuals received antidepressant medication after stepping-up from watchful waiting. Two further sensitivity analyses were performed, one set all drop-out rates from depression treatment to 15%, the other set them to 45%.

Two sensitivity analyses were performed that examined the annual diabetes review. In one analysis it was assumed that everyone attended the annual review and that this review always included a depression screen for individuals who were not currently receiving depression treatment. In a separate sensitivity analysis the probability that the annual review includes a depression screen was set to 60%.

A final sensitivity analysis used values of 98% and 86% for the sensitivity and specificity of the opportunistic screen (respectively).

### 5.18 Model validation

The model was assessed using three forms of validation as described below.

- Reproducibility of results: As the model is based on two previously published models, we aimed to reproduce results from the UKPDS and Tosh et al (2013) models.
- Internal validity: Parameters were varied to extreme values to ensure results changed in the expected direction.
- External validity: Predictions from the model were compared against the published literature on diabetes and depression in the UK.

Model predictions were also checked for face validity.

## 6. Results

### 6.1 Base-case results

Although 600,000 simulations were run, the results are presented for a cohort of adults (N=2,000,000) diagnosed with T2DM in England [193]. The cohort is followed over their lifetime.

#### 6.1.1. Number of diabetes-related complications

The model predicted that the cohort would experience 341,200 microvascular and 1,151,000 macrovascular diabetes-related complications over lifetime under current clinical practice (Table 26). Introducing collaborative care (Policy 1) would lead to a reduction of about 5,900 and 8,800 micro and macrovascular complications respectively. The potential reductions in DM complications when increasing opportunistic screening (Policy 2) was slightly lower (-5,100 for microvascular, and -8,000 for macrovascular events). Conversely when looking at the combined policies (Policy 3), the potential to avoid DM complications increases and the numbers avoided are estimated to be -9,300 and 12,800 for microvascular and macrovascular events respectively.

In terms of ranking, compared to current practice, the combined policy (Policy 3) avoids the greatest proportion of microvascular events (ranging between -2.02% for diabetic ulcers to -3.62% for renal failure) and the increase in opportunistic screening (Policy 2) provides the least (ranging between -0.75% for diabetic ulcers to -2.61% for renal failure). The percentage reduction for macrovascular complications is smaller but again, in general, Policy 3 provides the greatest potential benefit (between -1.1% and -1.2%), and Policy 2 provides the smallest (between -0.7% to -0.9%).

**Table 26: Number of diabetes-related complications predicted by the model under current practice and new policies**

| | Current practice | Policy 1 | Policy 2 | Policy 3 | Inc (CP vs. P1) | Inc (CP vs. P2) | Inc (CP vs. P3) |
|---|---|---|---|---|---|---|---|
| **Number of microvascular complications** | | | | | | | |
| Blindness | 116,237 | 114,360 | 115,070 | 113,287 | -1,877 | -1,167 | -2,950 |
| Renal failure | 68,633 | 66,840 | 66,890 | 66,150 | -1,793 | -1,743 | -2,483 |
| Diabetic ulcer | 69,320 | 68,803 | 68,633 | 67,920 | -517 | -687 | -1,400 |
| Amputation | 87,017 | 85,303 | 85,450 | 84,560 | -1,713 | -1,567 | -2,457 |
| Total | 341,207 | 335,306 | 336,043 | 331,917 | -5,900 | -5,164 | -9,290 |
| **Number of macrovascular complications** | | | | | | | |
| IHD | 277,880 | 275,627 | 276,923 | 274,883 | -2,253 | -957 | -2,997 |
| MI | 377,417 | 374,227 | 374,190 | 373,437 | -3,190 | -3,227 | -3,980 |
| Stroke | 274,880 | 273,010 | 272,980 | 271,650 | -1,870 | -1,900 | -3,230 |
| CHF | 221,130 | 219,640 | 219,250 | 218,587 | -1,490 | -1,880 | -2,543 |
| Total | 1,151,307 | 1,142,504 | 1,143,343 | 1,138,557 | -8,803 | -7,964 | -12,750 |

CP: Current practice. IHD: Ischaemic heart disease. MI: Myocardial infarction. CHF: Congestive heart failure. Policy 1 = Collaborative care; Policy 2 = Opportunistic screening; Policy 3 = both collaborative care and opportunistic screening. Inc = incremental

### 6.1.2. Number of depressive episodes

Over the lifetime, the model predicts 15,517,000 depressive episodes under current clinical practice (Table 27). Policy 2 (increase in opportunistic screening) and Policy 3 (collaborative care plus increasing opportunistic screening) are estimated to produce the largest numbers of depressive episodes, but both also have larger proportions of cases identified and therefore treated at approximately 87% compared to 51% for current practice and 51% for Policy 1 (collaborative care). Of note, the increase in number of depressive episodes associated with the policies is attributable to an increase in life expectancy.

**Table 27: Number of depressive episodes predicted by the model under current practice and new policies**

| | Current Practice | Policy 1 | Policy 2 | Policy 3 | Inc (CP vs. P1) | Inc (CP vs. P2) | Inc (CP vs. P3) |
|---|---|---|---|---|---|---|---|
| **Number depression episodes** (1,000) | | | | | | | |
| Total number | 15,517 | 15,598 | 15,563 | 15,605 | 80 | -46 | -88 |
| Identified/ treated | 7,937 | 7,983 | 13,547 | 13,588 | 46 | -5,610 | -5,650 |
| Unidentified/ untreated | 7,580 | 7,615 | 2,016 | 2,018 | 35 | 5,564 | 5,562 |

CP: Current practice. Policy 1 = Collaborative care; Policy 2 = Opportunistic screening; Policy 3 = both collaborative care and opportunistic screening. Inc = incremental

### 6.1.3. Life years, QALYs and depression-free years

Policy 3 (collaborative care plus increasing opportunistic screening) was associated with the largest increase in life years (Table 28) compared with current practice (27.1 million for current practice, 27.3 million for Policy 3). This is attributable to the fact that Policy 3 was estimated to avoid the largest number of diabetes related complications overall and in particular, avoided the greatest proportion of macrovascular complications (see Section 6.1.1).

Collaborative care was also associated with the largest gain in years with no depression compared with current practice (20.9 million years compared to 19.4 million years for current practice).

When life years were adjusted for quality of life, Policy 3 was associated with the largest gain in QALYs (with gains of 160,000 for Policy 1, 125,000 for Policy 2 and 294,000 for Policy 3). Again this can be attributed to the numbers of diabetes related complications avoided and the increase in depression free years (Table 28).

**Table 28: Summary of life years, QALYs and time free of depression predicted by the model under current practice and new policies**

| | Current practice | Policy 1 | Policy 2 | Policy 3 | Incremental (CP vs P1) | Incremental (CP vs P2) | Incremental (CP vs P3) |
|---|---|---|---|---|---|---|---|
| **Undiscounted (1,000)** | | | | | | | |
| Life years | 27,116 | 27,240 | 27,208 | 27,282 | 125 | 93 | 167 |
| QALYs | 16,612 | 16,773 | 16,737 | 16,906 | 160 | 125 | 294 |
| Time with no depression | 19,407 | 20,199 | 19,923 | 20,937 | 792 | 516 | 1,530 |
| **Discounted (1,000)** | | | | | | | |
| Life years | 19,515 | 19,580 | 19,564 | 19,601 | 65 | 49 | 86 |
| QALYs | 12,006 | 12,103 | 12,082 | 12,188 | 97 | 76 | 182 |

CP: Current practice. QALYs: Quality-adjusted life-years. Policy 1 = Collaborative care; Policy 2 = Opportunistic screening; Policy 3 = both collaborative care and opportunistic screening.

### 6.1.4. Health care costs

The lifetime management cost of diabetes related complications was estimated to be £10 billion under current clinical practice (Table 29), representing about 24% of the total cost incurred over a lifetime (£40 billion). The cost associated with the annual review represented about 22% of the total cost. Collaborative care and the opportunistic screening policy were associated with an increase in health care costs, mainly attributable to increases in costs for both diagnostic interviews and the management of depression.

**Table 29: Costs predicted by the model under current practice and new policies**

| Costs (2013 UK £1,000,000) | Current practice | Policy 1 | Policy 2 | Policy 3 | Incremental (CP vs P1) | Incremental (CP vs P2) | Incremental (CP vs P3) |
|---|---|---|---|---|---|---|---|
| Management complications | 9,833 | 9,644 | 9,459 | 9,428 | -190 | -374 | -405 |
| Annual review | 9,134 | 9,222 | 9,200 | 9,294 | 88 | 66 | 161 |
| Primary care management | 11,169 | 11,337 | 11,281 | 11,470 | 167 | 112 | 300 |
| Ongoing diabetes management (excluding GP) | 6,833 | 6,865 | 6,856 | 6,875 | 31 | 23 | 42 |
| Diagnostic interview | 1,271 | 1,320 | 5,588 | 5,840 | 50 | 4,317 | 4,569 |
| Opportunistic screening | 107 | 112 | 547 | 574 | 5 | 440 | 467 |
| Management of depression | 3,215 | 4,666 | 5,349 | 7,728 | 1,451 | 2,134 | 4,513 |
| **Total cost** | 41,562 | 43,165 | 48,281 | 51,209 | 1,603 | 6,719 | 9,647 |

CP: Current practice. Policy 1 = Collaborative care; Policy 2 = Opportunistic screening; Policy 3 = both collaborative care and opportunistic screening.

### 6.1.5. Incremental cost effectiveness ratio

Collaborative care was associated with an incremental cost effectiveness ratio (ICER) of £10,798 per QALY gained compared with current practice. The ICER for an increase in opportunistic screening compared with current practice was estimated to be £63,810 per QALY gained (Table 30). The ICER for collaborative care along with an increase in opportunistic screening compared with current practice was estimated to be £37,421 per QALY gained (Table 30).

Policies were compared using incremental analysis whereby the least effective was compared to the next least effective policy. Improvement in opportunistic screening was dominated by collaborative care. Compared to collaborative care, collaborative care with improved opportunistic screening had an ICER of £68,017.

**Table 30: Incremental Cost-Effectiveness Ratios (discounted, sorted by ascending cost)**

| | **Costs (2013 UK £1,000,000**) | **QALYs (1,000)** | **ICER** |
|---|---|---|---|
| Current practice | £29,626 | 12,006 | |
| Policy 1 | £30,676 | 12,103 | £10,798 |
| Policy 2 | £34,475 | 12,082 | Dominated by Policy 1 |
| Policy 3 | £36,431 | 12,188 | £68,017 vs Policy 1 |

QALYs: Quality-adjusted life-years. ICER: Incremental cost-effectiveness ratio. Policy 1 = Collaborative care; Policy 2 = Opportunistic screening; Policy 3 = both collaborative care and opportunistic screening.

### 6.1.6. Wider societal impact

The time off paid employment due to ill health avoided due to each of the three policies was relatively small (2,700 years for Policy 1; 2,100 years for Policy 2 and 6,000 for Policy 3). This is due to the fact that most of the population is over 65 years at baseline and therefore not in the working force (Table 31). The number of days received informal care was lowest for Policy 3 and Policy 1 (4.9 million), mainly due to the respective increases in life expectancy from the diabetes related complications avoided in the policies.

**Table 31: Wider societal impact**

| Current practice | Policy 1 | Policy 2 | Policy 3 | Inc (CP vs P1) | Inc (CP vs P2) | Inc (CP vs P3) |
|---|---|---|---|---|---|---|
| Informal care (1,000) | | | | | | |
| 4,975 | 4,947 | 4,953 | 4,898 | -27 | -22 | -77 |
| Days off sick | | | | | | |
| 173,271 | 170,545 | 171,139 | 167,296 | -2,725 | -2,132 | -5,975 |

CP: Current practice. Policy 1 = Collaborative care; Policy 2 = Opportunistic screening; Policy 3 = both collaborative care and opportunistic screening.

### 6.1.7. Prevalence of depression

Under current practice the prevalence of depression was predicted to more than double over ten years, from 15.4% to 31.7%. Each of the policies was associated with reductions in the prevalence of depression, with cumulative effects over time. Policy 3 was associated with the largest reductions, from 2.3% at year 1 to 6.2% at year 10. Policy 2 had the smallest reductions in the prevalence of depression over time, from 0.7% at year 1 to 2.3% at year 10.

**Table 32: Prevalence of depression over the first ten years, as predicted by the model under current practice and new policies**

| | Current Practice | Policy 1 | Policy 2 | Policy 3 | Inc (CP vs. P1) | Inc (CP vs. P2) | Inc (CP vs. P3) |
|---|---|---|---|---|---|---|---|
| Year 1 | 15.36% | 14.14% | 14.63% | 13.10% | -1.22% | -0.73% | -2.25% |
| Year 2 | 17.83% | 16.39% | 16.75% | 14.74% | -1.44% | -1.08% | -3.09% |
| Year 3 | 20.21% | 18.70% | 18.99% | 16.65% | -1.51% | -1.22% | -3.56% |
| Year 4 | 22.40% | 20.61% | 20.90% | 18.40% | -1.79% | -1.50% | -4.00% |
| Year 5 | 24.43% | 22.33% | 22.84% | 19.95% | -2.11% | -1.60% | -4.48% |
| Year 6 | 26.18% | 23.88% | 24.45% | 21.37% | -2.29% | -1.73% | -4.80% |
| Year 7 | 27.78% | 25.33% | 25.90% | 22.53% | -2.45% | -1.87% | -5.25% |
| Year 8 | 29.19% | 26.50% | 27.16% | 23.58% | -2.69% | -2.03% | -5.61% |
| Year 9 | 30.49% | 27.70% | 28.43% | 24.47% | -2.79% | -2.06% | -6.02% |
| Year 10 | 31.65% | 28.65% | 29.34% | 25.45% | -2.99% | -2.31% | -6.19% |

Note: the denominator is people alive at each time point.
CP: Current practice. Policy 1 = Collaborative care; Policy 2 = Opportunistic screening; Policy 3 = both collaborative care and opportunistic screening. Inc = incremental

### 6.1.8. Impact of having depression on lifetime quality-adjusted life years accrued.

Patients with major depression experienced a reduction in their quality of life. For current practice and each of the three policies, the reduction in lifetime QALYs due to having depression was calculated as the total time spent with major depression multiplied by its disutility (0.3; there was no disutility associated with minor depression). The discounted results are summarised in Table 33. For comparison, the discounted QALYs accrued by the cohort are also replicated from Table 28. Under current practice the cohort accrued approximately 12 million QALYs for current practice and each of the policies. The QALY loss due to depression was largest for current practice (1,746). If this QALY loss were removed then the lifetime QALYs accrued under current practice would increase by 14.5%. Each of the policies is associated with a reduction in lost QALYs, with the largest reduction for Policy 3.

**Table 33: Impact of having depression on lifetime quality-adjusted life years accrued.**

| Discounted values (1,000) | Current Practice | Policy 1 | Policy 2 | Policy 3 | Inc (CP vs. P1) | Inc (CP vs. P2) | Inc (CP vs. P3) |
|---|---|---|---|---|---|---|---|
| QALYs accrued | 12,006 | 12,103 | 12,082 | 12,188 | 97 | 76 | 182 |
| QALY loss due to depression (1,000) | 1,746 | 1,695 | 1,702 | 1,631 | -51 | -44 | -115 |

CP: Current practice. Policy 1 = Collaborative care; Policy 2 = Opportunistic screening; Policy 3 = both collaborative care and opportunistic screening. Inc = incremental

### 6.2 Sensitivity analysis

Twenty-nine sensitivity analyses were performed, varying the key model inputs. A full list of the sensitivity analyses performed is provided in Appendix 15, along with the resulting estimates of cost-effectiveness (lifetime costs and QALYs for the cohort). Below, the sensitivity analyses that had the greatest impact on results are discussed.

Three sensitivity analyses led to a change in the rankings of the policies. Halving the time until relapse for people with a history of depression improved the outcomes for Policy 2; it extendedly dominated Policy 1, with an ICER relative to current practice of £9,875. The ICER for Policy 3 relative to Policy 2 was £15,453. Doubling the time until relapse led to Policy 1 dominating both Policy 2 and Policy 3. The ICER for Policy 1 compared to current practice was £8,233. Decreasing the average number of GP appointments for individuals with depression, from eight to four, led to Policy 2 being extendedly dominated by Policy 3. The ICERs were: Policy 1 vs current practice (£12,837), Policy 3 vs Policy 1 (£51,359).

Under the base-case analysis, only Policy 1 has an ICER (relative to current practice) less than the £30,000 commonly used as a threshold for cost-effectiveness. There were five sensitivity analyses for which Policy 3's ICER (relative to current practice) fell below £30,000. These analyses (and their ICERs) were:

- Halve the time until relapse (£10,872).
- Hazard ratio for depression affecting diabetic complications = 1.5 for all (£17,99)
- Disutility due to major depression = -0.5 (£22,461).
- Hazard ratio for depression affecting diabetic complications = 1.5 for all (£26,062).
- Sensitivity of screening test is 98%, specificity is 86% (£26,807).

There were two sensitivity analyses for which Policy 2's ICER (relative to current practice) fell below £30,000. These analyses (and their ICERs) were:

- Halve the time until relapse (£9,875).
- Hazard ratio for depression affecting diabetic complications = 1.5 for all (£26,719)

In conclusion, the results of the one-way sensitivity analyses showed that the model results were the most sensitive to the estimated time until relapse, and the hazard ratio for depression affecting diabetic complications. Results were robust to the majority of the other parameters varied.

## 7. Discussion

### 7.1 Overview of work

To our knowledge, this is the first economic evaluation assessing the long-term impact of policies targeted at individuals with diabetes with comorbid depression in England. This study examined the impact of three policies: collaborative care, an increase in opportunistic screening and a combination of both collaborative care and increasing opportunistic screening. The model estimated that these enhancements to the current pathway of care for individuals with diabetes and comorbid depression have the potential to reduce both the number of depressive episodes in England, and the number of diabetes-related complications. All three policies were associated with an improvement in quality of life and an increase in depression-free years compared with current practice, but with an increase in health care costs. All three policies produced some benefits when looking at a wider societal perspective and were associated with a reduction in both the number of days off sick due to ill health and the need for informal care. Overall Policy 3, which examined the effect of introducing both collaborative care and increasing opportunistic screening together, was estimated to produce the greatest benefits in terms of both events avoided and depression free years. However, the incremental cost-effectiveness ratio (£37,421) comparing Policy 3 to current practice is above the cost per QALY currently considered cost-effective. In addition, when comparing across the policies, Policy 2 (improvement in opportunistic screening) is dominated by Policy 1 (collaborative care), and comparing Policy 3 with Policy 1, this policy would again not be considered cost-effective (with an ICER of £68,017) when assuming a willingness to pay threshold of either £20,000 or £30,000 per QALY. However, these estimates do not take into account the uncertainty surrounding both parameters and structural assumptions.

A systematic review of collaborative care interventions concluded that there was a paucity of robust evidence in this area, and existing evidence suggests that there is the potential to reduce depression at a cost considered to be cost-effective. However, these studies are based on short-term data from RCTs and do not look at the long-term implications of increasing life-expectancy and the subsequent diabetes related complications. When these are taken into account, our analyses suggest the potential to benefit from the depression free time is more limited.

As is normal in healthcare modelling, the mathematical model represents a simplification of reality and results from our analyses need to be interpreted in relation to the assumptions

used and evidence available. The model was developed with the aid of an advisory group supplemented by a review of the published literature and a meeting with current service users.

Due to a paucity of robust evidence to inform the model parameters, a number of assumptions were required. The uncertainty in the parameters were not captured in probabilistic sensitivity analyses and the estimated effect of the policies predicted by the model was small therefore the results presented need to be interpreted with caution. In the current model, the bi-directional relationship between depression and diabetes is modelled through diabetes-related complications. An approach incorporating changes in clinical variables such as HbA1c, blood pressure and weight would have been preferred but this was not possible due to the lack of robust evidence on these parameters. Risk of diabetes related complications are affected by long-term changes and/or control in HbA1c, and it is uncertain if a short-term benefit due to reducing time with depression will have a substantial effect on the risk of complications. It is possible that modelling changes in the individual risk factors to predict changes in risk may produce more robust estimates for numbers of diabetes-related complications, as changes in the different diabetes risk factors due to short term benefits of improving depression status may have different effects on the microvascular and macrovascular complications as suggested by the differences in the magnitude and significance of the covariates used in the different UKPDS equations. Whilst there is evidence of a bidirectional association between having diabetes and having depression, the causal mechanisms that drive this association are likely to be complex and are the subject of active research.

There is structural uncertainty in the method used to depict the natural history of depression and the impact of subsequent treatment. Sensitivity analyses on related parameters did not show a large effect on results which suggests that any potential benefit from a policy reducing the time with depression, or a policy increasing identification, was limited. There may be additional benefits attributable to the policies which are not captured in the model. For example, for collaborative care, patients may gain an increase in satisfaction with their health care management and thus will be better able to control their diabetes medications whilst being depressed.

### 7.2 Research implication

Whilst the results generated from the model are encouraging and suggest the proposed policies may potentially be a cost-effective use of NHS resources, additional research is

required to decrease the uncertainty in the results presented. Existing meta-analyses suggest that the change in glycaemic control associated with interventions directed at depression may be relatively small. However, research examining the effect of depression interventions on variables such as BMI, blood pressure etc, is required to determine the effect on other known risk factors. There is also a paucity of evidence on the natural history of depression in patients with diabetes. Further research is required to understand the duration, frequency and progression of depression in these patients. Research examining the effect on health related quality of life of depression in patients diagnosed with diabetes and diabetes related complications is also required. Whilst there is some evidence suggesting a link between depression and diabetes complications, the exact causality is unclear. Further research is required to understand how the presence of diabetes related complications impact on the incidence and relapse of depression in terms of both the size of effect and the duration. Further understanding is required on the additional health care resource use for patients with diabetes who are depressed.

### 7.3 Policy implication

A policy which increases opportunistic screening could be introduced as a mandatory requirement or could be achieved as a result of a campaign for increasing awareness targeted at the relevant healthcare professionals. Either of these alternatives would have an associated cost which has not been included in the current analyses.

While this study examined the effects of policies in patients with diabetes, the proposed changes to the pathway are potentially generalizable to patients with alternative long term physical conditions predominantly treated within primary care. Patients with diabetes are at high risk of both microvascular and macrovascular events and a substantial proportion of the additional costs associated with the policies explored here are offset by the costs of the diabetes complications avoided. However, many other long-term physical conditions elevate the risk of additional comorbidities, and there is the potential to avoid health care costs across the spectrum of the NHS. For example, chronic obstructive pulmonary disease (COPD) has been identified as a chronic condition that is one of the largest contributors to preventable hospital admissions and people with COPD and other respiratory conditions have an increased risk of diabetes compared to the general population.

The majority of existing models assess the policy implications for single conditions in isolation. The results from the current analyses suggest that benefit from these models may be under-estimated because the impact of multi-morbidity is not taken into account.

## 8. Conclusion

Using the evidence currently available, the results of this research suggest that policies targeted at identifying and treating depression early in patients with diabetes may lead to a reduction in diabetes related complications and depression, which in turn increase life expectancy and health related quality of life. Although there is an increase in overall health care costs, the results show this is below the willingness to pay threshold currently considered acceptable in England.

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