Prevention of type 2 diabetes: risk identification and interventions for individuals at high risk

Economic Review and Modelling

Commissioned by:	NICE Centre for Public Health Excellence
Produced by:	ScHARR Public Health Collaborating Centre
Authors:	Mike Gillett, Research Fellow (Modeller) Jim Chilcott, Technical Director Public Health Collaborating Centre Liddy Goyder, Professor of Public Health Nick Payne, Associate Director, NICE Public Health Collaborating Centre Praveen Thokala, Health Economist Crystal Freeman, Systematic Reviewer Maxine Johnson, Systematic Reviewer Helen Buckley Woods, Information Specialist
Correspondence to:	Vivienne Walker School of Health and Related Research (ScHARR) University of Sheffield Regent Court 30 Regent Street Sheffield S1 4DA v.walker@sheffield.ac.uk

About the ScHARR Public Health Collaborating Centre

The School of Health and Related Research (ScHARR), in the Faculty of Medicine, Dentistry and Health, University of Sheffield, is a multidisciplinary research-led academic department with established strengths in health technology assessment, health services research, public health, medical statistics, information science, health economics, operational research and mathematical modelling, and qualitative research methods. It has close links with the NHS locally and nationally and an extensive programme of undergraduate and postgraduate teaching, with Masters courses in public health, health services research, health economics and decision modelling.

ScHARR is one of the two Public Health Collaborating Centres for the Centre for Public Health Excellence (CPHE) in the National Institute for Health and Clinical Excellence (NICE) established in May 2008. The Public Health Collaborating Centres work closely with colleagues in the Centre for Public Health Excellence to produce evidence reviews, economic appraisals, systematic reviews and other evidence based products to support the development of guidance by the public health advisory committees of NICE (the Public Health Interventions Advisory Committee (PHIAC) and Programme Development Groups).

List of Abbreviations

CHD	Coronary Heart Disease
CKD	Chronic Kidney Disease
CVD	Cardiovascular disease
CRS	Cambridge Risk Score
IGR	Impaired Glucose Regulation
DPP	Diabetes Prevention Program
DPS	Diabetes Prevention Study
FINDRISC	Finnish Diabetes Risk Score
FPG	Fasting Plasma Glucose
FSG	Fasting Serum Glucose
GCT	Glucose Challenge Test
HRQoL	Health-related Quality-of-Life
IFG	Impaired Fasting Glucose
IGR	Impaired Glucose Regulation
IGT	Impaired Glucose Tolerance
LPDS	Leicester Practice Database Score
LSA	Leicester Self-Assessment Score
NGT	Normal Glucose Tolerance
OGTT	Oral Glucose Tolerance Test
OHAs	Oral Hypoglycaemic Agents
PDG	Program Development Group
QALY	Quality-adjusted Life Year
RCT	Randomised Controlled Trial
UKPDS	UK Prospective Diabetes Study
WHO	World Health Organization

Terminology

This report is concerned with the identification and management of individuals at 'high risk of diabetes'. Although how to define "high risk of diabetes" is arguable, for the purpose of this document, this term is used interchangeably with the term 'Impaired Glucose Regulation (IGR)'. The term pre-diabetes was commonly used in earlier studies to refer to individuals with IGR but is not conventionally used any longer so we do not use this term (except in reference to such previous studies).

TABLE OF CONTENTS

List of Tables

List of Figures

Executive Summary

Introduction

This report starts by summarising the existing evidence in respect of the cost-effectiveness of risk assessment and intervention for individuals at high risk of diabetes. It then goes on to describe in detail the methods for producing scenarios for a range of risk assessment strategies <u>and</u> associated interventions to prevent progression to diabetes.

A wide range of risk assessment strategies was examined initially, but these have been narrowed down to a smaller number after consideration of their key characteristics. A number of intervention strategies, with a range of costs and intensities, have then been examined in combination with these risk assessment strategies. Economic modelling was used to estimate the lifetime cost-effectiveness interventions to prevent diabetes in high risk individuals identified through alternative risk assessment strategies.

Results from Review of the Existing Literature

Despite the wide range of assumptions made about baseline risk and relevant costs, cost-effectiveness studies and a number of recent systematic literature reviews consistently report that risk assessment for pre-diabetes is highly likely to be cost effective in the populations considered, even at a threshold of £10,000 per QALY or less.

Modelling and Main Modelling Assumptions

A combination of decision tree and Markov methods was used to model the risk assessment and intervention components, respectively. The aim was to produce cost-effectiveness ratios for the combination of risk assessment and intervention.

Scenario-based analyses were carried out in respect the 'cut-points' (i.e. thresholds for further action) for both risk assessment tools and blood tests; and a range of interventions of varying intensity were modelled.

The assumptions for the modelling are described in detail in the main report, but the key ones are listed here:

- Current practice was taken to be the NHS Health Check programme protocol - i.e. risk assessment and diagnosis based on a fasting blood glucose (FBG) and oral glucose tolerance test (OGTT) for diagnosis of diabetes (and implicitly Impaired Glucose Regulation (IGR)) but no interventions for those identified with IGR;

- Risk assessment was assumed to involve a combination of a risk assessment tool using either a self-completion questionnaire or routine primary care data, together with blood tests for those identified at possible increased risk;

- The blood tests considered were fasting blood glucose or HbA1c;

- It was assumed that oral glucose tolerance tests (OGTT) would not be used to confirm diagnosis of Impaired Glucose Regulation (IGR) for the alternative strategies to the NHS Health Check;

- In addition to detection of IGR, it was assumed that cases of diabetes would also be identified and treated earlier;

- The intensity and associated effectiveness of the interventions was varied between the full effect seen in the major intervention trials and a more modest effect seen when these were translated into a low intensity 'real-world' clinical practice intervention;

- Varying assumptions about the maintenance element of the intervention and of the duration of overall effect (on weight loss) were made;

- The effects on survival and co-morbidities were modelled over a lifetime to produce estimates of total quality adjusted life years (QALYs);

- Included in the consideration of costs were the direct NHS costs of risk assessment, costs of delivering the components of intervention in respect of IGR, costs of subsequent monitoring and treatment of diabetes and its associated complications;

- After obtaining discounted costs and QALY estimates, incremental cost-effectiveness ratios for the each of the risk assessment/intervention scenarios were calculated.

Results from Modelling

The results show that the cost-effectiveness is largely determined by the intensity of the intervention employed and choice of cut-points for diagnosis and intervention. The overall prevalence of IGR and diabetes were found to be extremely sensitive to the choice of scores/tests and associated cut-points used for diagnosis.

The most cost-effective strategies are likely to involve risk assessment followed by a relatively intensive intervention. The modelling suggests that a wide range of risk assessment/intervention strategies are cost-effective (compared with a policy of risk assessment without intervention for IGR) at usual cost-effectiveness thresholds, and therefore that policy/commissioning decisions are likely to be influenced by other criteria such as total cost to the NHS.

Overall, the most cost-effective strategies with the greatest health gains involve risk scoring using routine primary care data rather than self-assessment questionnaires (because of uptake levels of the latter), in combination with a blood glucose test for risk assessment and diagnosis followed by as intensive lifestyle

intervention as feasible. However, where routine primary care data are not available, particularly in settings outside a primary or secondary care setting, such as a pharmacy, shopping centre, community or religious centre or the internet, the use of self-assessed risk scoring should not be precluded.

As South Asians are at greater risk of diabetes and some diabetes-related complications (e.g. CHD), we also modelled the cost-effectiveness of risk assessment and intervention in a younger South Asian cohort, of age 25-39. For this group, risk assessment and intervention was found to be even more cost effective (and probably cost saving).

Conclusions

Based on existing evidence and the modelling carried out for this review, risk assessment for undiagnosed IGR (and diabetes) followed by intervention in high risk individuals is highly likely to be cost-effective compared to identification of undiagnosed diabetes alone within the current Vascular Checks program. The most cost-effective strategy is likely to involve:

- Use of routine primary care data as a first step in the risk assessment process but where this is not possible, self-assessed risk scoring may substitute for routine primary care data
- Using HbA1c or FPG as both a subsequent risk assessment and confirmatory diagnostic test
- Use of relatively intensive lifestyle interventions followed by a maintenance component

Although less certain, the available evidence also suggests:
- Use of metformin if an individual at high risk of diabetes fails to achieve an adequate response to lifestyle targets (i.e. change in weight and/or physical activity);
- An interval of three to five years for repeat testing (for those who would not otherwise be recalled sooner).

We have suggested a simple, pragmatic method of prioritising interventions for those at highest risk, which will increase overall cost-effectiveness and can be used to ensure optimal targeting of scarce resources.

All of these results and conclusions are based on assumptions about the effectiveness of interventions in populations identified by strategies (HbA1c or FPG test) that differ from the original intervention studies, and therefore should be treated with caution until evidence from further research is available.

Note :
The Leicester Practice Risk Score (LPDS) algorithm used in the economic analysis has subsequently been modified during academic peer review prior to publication. **Therefore, the identification of target individuals for glucose testing from GP practice data, including the choice of cut-point, should use the final published algorithm (Gray 2012 [1]).**

1. HEALTH ECONOMIC REVIEW OF RECENT ECONOMIC MODELS OF RISK ASSESSMENT AND MANAGEMENT OF UNDIAGNOSED IGR

1.1 Introduction

The economic evidence for risk assessment and intervention strategies comes from both the existing cost-effectiveness evidence base and the model results. This section of the report reviews recently published economic models which address the cost-effectiveness of risk assessment and management of IGR.

The previous economic modelling in this field helps to inform the additional modelling required to be undertaken to support the development of guidance and allows the modelling results to be considered in the context of previous reports on cost-effectiveness.

Since a large number of relevant economic models in this field and systematic reviews of those models have been published relatively recently which cover the earlier literature (pre 2005), we have focused on identifying the recent papers in this field (from 2005) in order to highlight how their structure, assumptions, data sources and findings differ from the ScHARR model described in this report. Relevant models were those that addressed the review question, i.e. risk assessment for both diabetes and IGR.

It is notable that the models identified by reviews published in 2007 (and before) examined *either* the cost-effectiveness of risk assessment for diabetes (without including the potential costs and benefits of intervention in those who will be identified by the assessment procedure as having lesser degrees of IGR *or* the cost-effectiveness of interventions to reduce the risk of progression after IGR has already been diagnosed (i.e. without including the costs and additional benefits of the risk assessment process, which may also identify undiagnosed diabetes).

In order to examine more fully the realistic options for risk assessment and earlier intervention, and examine trade-offs between earlier and later interventions, more recent models have examined the potential costs and benefits from interventions that both identify and intervene in IGR or in both diabetes and IGR.

This review therefore focuses on models and reviews which have addressed three key questions:

- *What is the likely cost-effectiveness of interventions to identify and manage IGR?*
- *What are the main factors which will influence the cost-effectiveness of risk assessment and intervention in IGR?*
- *Is it more cost-effective to identify and actively intervene in screen-detected IGR or screen-detected diabetes, or both, given that any risk assessment programme will identify both?*

1.2   Methods

Studies were identified through the review search strategies which included searching in the NHS Economic Evaluation Database (via Wiley). Further simplified search strategies were also used to search other economic specific databases, both EconLit (via OVID SP) and the Health Economic Evaluations Database (HEED). The search strategy is included in Appendix 1. A date limit of 1998 to current (mid-2011) was applied in order to retrieve evidence that coincided with the publication of the latest WHO diagnostic criteria. The Public Health Interventions Cost Effectiveness Database (PHICED) which is part of the National Library for Public Health was also searched using terms including screening, diabetes and pre-diabetes.

In addition to the above, targeted searches may be undertaken for model parameters and existing models. This process built on the ScHARR team's existing knowledge of the relevant literature and took the form of citation searching, reference tracking and consultation with experts.

Inclusion criteria: Papers which have used quantitative cost-effectiveness models to address the key questions listed above and have considered the long term impact on both costs and benefits of risk assessment for IGR and diabetes.

1.3   Results

1.3.1 One-off Risk assessment followed by intervention

There are four relevant reviews, including three HTA monographs, which have reviewed cost-effectiveness models for diabetes screening or for earlier intervention in IGR to reduce risk of progression (Karnon et al 2007 [2], Waugh et al [3], Gillett et al [4] and Lauritzen et al [5]). However the most recently published systematic review of diabetes prevention studies, Lauritzen et al [5], only included two cost-effectiveness studies Herman et al 2005 [6] and Eddy et al 2005 [7].

We therefore considered for inclusion all primary modelling studies published since 2005 and included those which address the three key questions above.

There are four cost-effectiveness models published in the last three years that meet the inclusion criteria. Many other papers examine specific elements of the potential costs (or costs and benefits), of earlier intervention. However only Gillies et al [8], Colagiuri & Walker 2008 [9], Chatterjee et al [10] and Schaufler and Wolff [11] include costs and benefits of identifying and treating both IGR and diabetes. This may be because, though it is inevitable that any risk assessment programme will identify both, the evidence from large RCTs for early intervention in IGR remains more robust than the evidence for early intervention in diabetes (for which there is a lack of RCT evidence).

The population, risk assessment strategies, key assumptions and findings of the models are outlined below in Table 1.

A table of health economic papers 2005-2010 excluded from further review, and a table of papers only considering benefits from diabetes prevention (rather than an overall program of identification, prevention and earlier diagnosis) are shown in Appendix 2.

Despite the wide range of assumptions made about baseline risk and relevant costs, cost-effectiveness studies and a number of recent systematic literature reviews generally report that screening and intervention for IGR is highly likely to be cost effective in the populations considered – at a threshold of £10,000 per QALY or less.

In the case of Colagiuri & Walker 2008, it should be noted that the cost per QALY is relatively high because of the short 10 year horizon from initial screening, resulting in many benefits later in life being excluded.

Table 1 : Publication, scenarios modelled and key results

Author / Country/Year	Population	Screening strategy	Eligibility for intervention	Risk reduction intervention	Costs & outcomes included	Results
Gillies et al/UK/ 2008 [8]	45 year olds in UK population	One-off screening with FPG followed by 2 hr OGTT	1. T2DM 2. IGT or T2DM	a. lifestyle modification b. drugs (metformin)	Screening and intervention costs; QALYs	Cost (£)/QALY versus 'No screening' 1. 14,150 (T2DM only) 2a. 6242 (T2DM or IGR with lifestyle modification 2b. 7023 (As for 2a but with metformin, not lifestyle modification)
Colagiuri & Walker /Australia/ 2008 [9]	55-74 year olds + 45-54 year olds with 1 or more risk factors	One off screening of 50% of population with FPG followed by 2 hr OGTT	IGT and T2DM	Lifestyle modification only	Screening and intervention costs; DALYs; 10 year horizon from initial screening	AU$/DALY 50 000
Schaufler & Wolff/ Germeny/ 2010 [11]	35-75 year olds in German population covered by statutory health insurance	Annual screening with OGTT (not otherwise specified)	IGT or IFG or T2DM	a. lifestyle modification b. drugs (metformin)	Lifetime costs of screening and intervention; QALYs	Euros/QALY (2006 values) a. 563 b. 325
Chatterjee et al/US/ 2010 [10]	Average age 48 years; BMI >=30;	One off screening with	IGT or IFG	a. lifestyle modification	Screening and intervention costs; 3-	All interventions cost-saving

	55% African American	1. GCT-pl (1hr post glucose)	or	b. drugs (metformin)	year horizon	
		2. GCT-cap	T2DM			
		3.RPG				
		4.RCG				
		5. HbA1c				

T2DM = Type 2 diabetes, IGT = Impaired Glucose Tolerance, IFG = Impaired Fasting Glucose, IGR = Impaired Glucose Regulation

Table 2 : Sources of model parameters and key model assumptions

Author / Year	CVD risk engines used for : a) NGT b) IGT c) T2DM	Baseline assumptions re progression from IGT to T2DM; Glucose progression assumptions from onset of diabetes to clinical diabetes	Intervention [comparator] to prevent diabetes, duration, intvn cost, clinical effectiveness (source of evidence ?)	Durability of risk (or weight) reduction	Approach to modelling burden of diabetes, e.g. Markov, decision tree, life table;	Assumptions re 2nd line OHA therapy for T2DM (if reported); Assumptions re statin therapy for T2DM	Any non-vascular complications included ? QoL benefits relating to weight reduction included ?	Perspective (e.g. NHS, societal); Discount Rate for Costs & Benefits; Horizon	Inc Costs, Incr QALYs, ICER	Key factors driving cost effectiveness (e.g. as shown from sensitivity analyses)
Gillies et al 2008	Not separately modelled	Per 100 person yrs Value (se): *Normal to IGT* <65yrs 1.66 (0.08) >65yrs 2.49 (0.11) *IGT to DM* 1.96 (0.25) *DM undetected* 1.65 (0.68) years	Based on Gillies systematic review	Not reported	Decision tree + Markov model	Not reported	Not reported	NHS costs per QALY gained	1. Cost per QALY 2. Probability of cost-effectiveness based on WTP thresholds £20K/£30K	1. Prevalence of DM and IGT 2. Compliance with intervention
Schaufler & Wolff 2010	Not separately	Not reported	Based on DPP	Not reported	Decision tree + Markov	Not reported	Not reported	Health care costs/savings per QALY	1. Cost per QALY	Discount rate Participation rate

	modelled		results		model			gained		
Chatterjee et al 2010	Not separately modelled	10%/yr with IGT; 15% with IGT&IGF.	Based on DPP results	Not reported	Costs and savings directly estimated	Not reported	Not reported	Both health system + societal perspective reported	Costs only	1. Prevalence of DM and IGT 2. Costs of false-negatives

1.3.2 Re-screening Interval

Economic evaluation of optimal re-screening intervals entails considerable modelling complexity. Specifically, data is needed on progression rates in those that screen negative at first screen, and progression and regression rates between NGT and IGR . For these reasons and due to time constraints we have not been able to model the re-screening interval but have presented the existing literature on this in Section 1.3.2.

There are a number of modelling studies [8], [12], [13], [14]. [15], [16], [17] that examine the effect of different re-screening strategies but there is only one primary study [12] which directly examined re-screening intervals in a patient cohort.

Lindeman et al [12] performed a study to determine the necessity for screening healthy elderly (> 65 years) every 3 years using fasting serum glucose (FSG) determinations. Participants (initially healthy, upper middle class, community-based volunteers, mostly age 65 years and older) were followed longitudinally with annual FSG concentrations and body mass indices (BMI) for periods up to 18 years (mean 12.4 years). It was observed that FSGs tended to decrease with age; more participants (220) had a negative slope than positive slope (79) when FSGs were plotted over time (years) for each individual. The authors concluded that it is not necessary to screen non-obese persons (excluding minorities) over 65 years of age who have a baseline fasting glucose of less than 100 mg/dl, and it is not necessary to screen persons over age 75 years every 3 years.

There are several modelling studies that examine screening intervals. Kahn et al [13] used the Archimedes model to compare eight simulated screening strategies for type 2 diabetes with a no-screening control strategy. Strategies differed in terms of age at initiation and frequency of screening and these differed substantially in the number of QALYs gained. Five screening strategies had costs per QALY of about US$10,500 or less, whereas costs were much higher for screening started at 45 years of age and repeated every year ($15,509), screening started at 60 years of age and repeated every 3 years ($25,738), or a maximum screening strategy (screening started at 30 years of age and repeated every 6 months; $40,778). The authors conclude that screening for type 2 diabetes is cost effective when started between the ages of 30 years and 45 years, with screening repeated every 3–5 years.

Gillies et al [8] extended their Markov model which only had one-off screening at age 45 to assess the impact of having one or two additional screenings, at age 50 and 60. The authors applied the base case test sensitivities to the numbers in the states of undiagnosed impaired glucose tolerance and type 2 diabetes at the corresponding time period. However, there was little variation in the cost-effectiveness of the different number of screenings; the cost per QALY for the base case scenario (i.e. one-off screening at age 45) was £3,429 and the cost per QALY for three screenings (base case plus two additional screenings, at age 50 and 60) was £3,517.

Johnson et al [14] also estimated the efficacy and cost of alternative strategies for systematic screening for type 2 diabetes by simulating alternative DM2 screening intervals (1, 3, and 5 years) and random glucose cut-off levels (100, 130, and 160 mg/dl) for the US population aged 45 to 74 years. They concluded that screening every 3 years with a random glucose cut-off of 130mg/dl provided optimal yield and minimized false-positive test results and screening costs.

A five-state illness-and-death Markov chain model was used by Kuo et al [15] (transition parameters were estimated using data from two rounds of a blood sugar screening programme for NIDDM in Puli, in central Taiwan) to assess the efficacy of screening for NIDDM for different screening frequencies (annual, biennial, 4-yearly and the control group). They found no significant difference in benefit between screening intervals less than three years and concluded that a 4-yearly screening regime for NIDDM would be most effective and feasible in Taiwan.

Park et al [16] undertook a study to quantify the proportion of people diagnosed as having type 2 diabetes by standard 75g oral glucose tolerance test, in a hypothetical screening programme, who would actually be false positives. The authors aimed to estimate the effect of varying the time between repeat screens on the false positive percentage and on the duration in person years of exposure to undiagnosed disease. They reported that reducing the screening interval from 4 years to 1 year increases harm in terms of false positives and the potential disadvantages of a false label.

The Scottish Public Health Network recommends a three year interval for re-screening but admits that data on the optimal interval are lacking. They believe that the time period for re-screening could be potentially refined by combining the HbA1c value with other risk measures to better define likely future trajectory.[17]

Takahashi et al [18] reported that screening at shorter intervals than 3 years in those with an HbA1c <6.0% is likely to identify few patients (less than 1%) with an HbA1c of at least 6.5%. However, risk of progression in those with an HbA1c above 6.0% is high and warrants at least annual monitoring.

Many newly identified IFG patients progress to diabetes within 3 years, which has been suggested as a recommended screening interval [19].

Thus, despite a number of modelling studies looking at screening intervals, it is difficult to report a precise optimal screening interval. This can be attributed to the heterogeneity of patients, risk equations, etc which reduces the comparability of the studies. However, based on these studies, re-screening every 3-5 years would seem reasonable.

1.4   Discussion

Existing economic studies contain a wide range of assumptions made about baseline risk and relevant costs and so formal quantified synthesis of results is not appropriate. However, it is notable that despite the wide range of assumptions made about baseline risk and relevant costs, cost-effectiveness studies consistently report that screening for IGR is highly likely to be cost effective – this includes the analysis by Gillies et al which is the most relevant (and UK-based) study as it included screening for IGR and diabetes, as well as interventions to prevent diabetes.

This suggests that the main value in further modelling may lie in modelling the specific risk assessment strategies that are considered to be the most feasible (acceptable and affordable) and exploring how both the public health impact and cost-effectiveness of risk assessment might be optimised (as this may influence guidance on choice of risk assessment and intervention strategies). This is considered more useful than obtaining more accurate estimates of cost-effectiveness of any specific strategy which would likely just confirm that they are cost-effective (assuming similar assumptions to existing models).

Further modelling is needed to explore a number of key assumptions that will impact on cost-effectiveness. These include :

- considering the impact of less intensive lifestyle intervention than those delivered within large-scale randomised diabetes prevention trials
- a management model that can incorporate the impact of comprehensive cardiovascular risk management
- risk assessment and diagnostic strategies including the use of HbA1c and fasting blood glucose, as an alternative to strategies that use an oral glucose tolerance test (OGTT) as the gold standard for diagnostic testing

It is worth noting the study by Ackermann 2006 in which the prevention program involved a cost-sharing scheme with the aim of incentivising participants to adhere to lifestyle goals [20], these having been shown to be the key determinants of successful prevention [21, 22].

2. ECONOMIC MODELLING - METHODS

2.1   2.1   Overview

Figure 1 : Logic Framework for economic modelling

Prevention of Diabetes Logic Framework

Pathway

Evidence needs & considerations

Risk score (Pre-screen)

Identify **using risk score**, eg Leics. Self-Assesst Score, Leics Practice Database Score, Cambridge Risk Score

Which **risk scoring tool ?** What **cut-off ?**

Long-term **risk of diabetes** by **baseline risk score**

Invited for HbA1c / FPG test
Population at highest risk of prediabetes/ diabetes

Which test ?

Prioritising testing intervention given constraints on access to intervention (financial, manpower)

Variation in uptake in different

Test Result

Threshold for diagnosis of IGR

Type 2 Diabetes

Normal Glucose tolerance

IGR / High Risk

Refine **risk estimate** (given IGR)

Risk stratification method ? What algorithm / cut-off ?

NICE Type 2 Diabetes Treatment Pathway

Lowest risk for progression

Low risk for progression

High risk for progression

Timing Impact of early vs late intervention on risk of progression

diet & exercise intervention strategies 'real world' culturally-adapted adaptations of intensive large prevention trials that are –
- still effective / cost-effective ?
- viable (affordable & enough trained staff to deliver in the 'real-world') ?
- provide some form of ongoing maintenance (eg counselling) ?

Monitoring / basic advice, or 'light' community intervention

Patient responds eg weight loss

Inadequate response

Uptake & adherence

Drugs (eg metformin)

Figure 1 above shows the key issues that are addressed by the modelling and the relationship between them.

2.2   Detecting Undiagnosed IGR and Diabetes

2.2.1 Prevalence of Undiagnosed Type 2 diabetes and those at High-risk

2.2.1.1 Estimates based on conventional FPG/OGTT definition

Based on the 2011 Association of Public Health Observatories (APHO) Diabetes Prevalence Model (Table 1) [23], the prevalence of undiagnosed diabetes (Type 1 and Type 2) in England is 1.8%. As approximately 90% of these are Type 2 [23;23], there is an estimated 1.6% prevalence of undiagnosed Type 2 diabetes.

The prevalence of Impaired Glucose Tolerance (IGT) or Impaired Fasting Glucose (IFG), collectively referred to as Impaired Glucose Regulation, in the European DECODE study was 19% , with similarly high rates being shown from other studies [24]. Most of these cases are undiagnosed, with a prevalence 16% being reported from a UK multi-ethnic community screening study [25].

The prevalence of undiagnosed cases in younger age groups (those below 40) is less well-known.   One way to estimate the prevalence for younger groups is based on linear extrapolation of rates within age bands of the 40-74 group. This is considered reasonable given an analysis by Saaristo [26] which suggests that prevalence is reasonably linear with FINDRISC value, of which age in a major determinant.

2.2.1.2 Estimates using HbA1c to define diabetes and IGR

Using an HbA1c test with the following cut-points gives the following prevalence of undiagnosed diabetes and IGR in the UK multi-ethnic LEADER cohort [25].

- Type 2 diabetes (HbA1c ≥ 6.5%) : 5.8% (versus 3.3% for OGTT-defined diabetes)IGR (HbA1c 6.0-6.4%) : 18.5% - this is similar to the OGTT-defined prevalence in that cohort (and the rates above in Section 2.2.1.1)IGR (HbA1c 5.7-6.4%) : 45%

The prevalence may be lower in an average UK cohort with lower ethnic prevalence. Age can also affect the prevalence – the average age in this cohort was 57.

2.2.2 Access To Risk assessment – Alternative Access Points

Although the core modelling relates to the 40-74 age group eligible for the NHS Health Checks programme, risk assessment may not necessarily be restricted to this group. For example, risk assessment may also be important in other high risk groups, for example South Asians aged 25-39 who are at risk of diabetes at a younger age, so a separate analysis has been undertaken for this group.

2.2.3 Blood glucose definitions of Impaired Glucose Regulation (IGR) and Diabetes

2.2.3.1 Definition of IGR and Type 2 Diabetes

At the start of this project, the World Health Organization (WHO) had yet to publish its revised recommendations on the diagnosis of diabetes and IGR. The 2006 World Health Organization criteria (WHO) for pre-diabetes were :

- Impaired fasting glucose (IFG) – Fasting plasma glucose (FPG) between 6.1 and 6.9 mmol/litre
- Impaired glucose tolerance (IGT) – FPG less than 7.0 mmol/litre and a plasma glucose (2 hours after ingestion of a 75 g oral glucose load, the oral glucose tolerance test) between 7.8 and 11.0 mmol/litre

One major reason for undiagnosed cases is that current tests in practice require overnight fasting, and many patients either do not like fasting or they just forget to fast before the test. However, with the need for tests that are convenient for people and that provider eligible results, over recent years the debate has moved towards whether HbA1c can be used for a diagnosis, and does not require patients to fast.

The WHO guidance was published early in 2011, with a recommendation to use an HbA1c test with a cut-off ≥ 6.5% for a diagnosis of Type 2 diabetes but made no recommendation for an equivalent cut-off for IGR [27].

Throughout this report, HbA1c will be reported on the DCCT- HbA1c % scale rather than the newer IFCC-HbA1c mmol/mol scale. Conversion is possible using the following formula:

> IFCC-HbA1c (mmol/mol) = [DCCT-HbA1c (%) - 2.15] x 10.929

It important to compare the cost-effectiveness of testing using an HbA1c test versus a fasting plasma glucose test (FPG). Either strategy would maintain the requirement for two positive tests to confirm a diagnosis of diabetes.

There remained two important related questions which would influence the modelling approach:

1) How should the performance of HbA1c or FPG-based testing be assessed -

  i) determine true & false test results from HbA1c or FPG-based testing with reference to the OGTT as the 'gold standard' (i.e. with false positives and false negatives)
  ii) define diabetes by the cut-point for HbA1c or FPG, i.e. and therefore assume that the tests are 100% sensitive and specific with no false positives or false negatives

2) How should the condition IGR or being at high risk of diabetes be defined?

The PDG came to the conclusion that diabetes should be defined by the appropriate cut-point for HbA1c or FPG, and that the OGTT result was not relevant for this purpose.

2.2.3.2 Assessment of performance of HbA1c or FPG-based testing

There was initially a lack of data on risk assessment outcomes using a risk score in conjunction with FPG or HbA1c as the definition of diabetes. Also, from a modelling view point, for a 'fair' assessment of alternative

risk assessment strategies based around varying definitions of diabetes, consideration is needed as to whether –

- the distributions of risk of diabetes of individuals classified as IGR are comparable between alternative risk assessment strategies
- the response to interventions to prevent diabetes are similar between alternative risk assessment strategies (i.e. similar to rates observed in large RCTs in which individuals are often recruited on the basis of an OGTT (with many as a result of elevated 2-hour glucose rather than elevated fasting plasma glucose)

Where HbA1c or FPG is used as the diagnostic test, without use of OGTT, it would appear to be inappropriate to determine "true" & "false" test results from HbA1c or FPG-based testing with reference to the OGTT as the 'gold standard'.

However it should be considered that since FPG, HbA1c and OGTT identify different populations of IGR, it may not be appropriate to assume that the outcomes of strategies using different diagnostic criteria can be regarded as equivalent.

2.2.3.3 Definition of IGR/High risk of diabetes

The modelling compares the cost-effectiveness and other outcomes from using alternative HbA1c and alternative FPG cut-points to separate individuals with normal glucose tolerance (NGT) from those with IGR. A single FPG or HbA1c test has been regarded as sufficient to identify IGR without the need for a second confirmatory test (OGTT or otherwise). This is because IGR is a metabolic condition rather than a disease, unlike diabetes (for which a second test is necessary in order to rule out measurement error or individual variation causing an abnormal first result).

Table 3 : Number of tests required to identify IGR and diabetes

No. of tests needed	HbA1c	FPG
Label as IGR/High-risk (see note 1)	1	1
Diagnose T2DM (see note 2)	2	2

2.2.4 Strategies To Identify Undiagnosed IGR and Type 2 Diabetes - options

2.2.4.1 Stepped approach to obtaining a set of algorithms for full economic evaluation

Risk assessment can involve a variety of tools (e.g. a risk score or algorithm such as the Cambridge Risk Score (CRS) [28] or Leicester Self-Assessment Score (LSA) [29] and glucose tests (e.g. HbA1c, FPG, Random Glucose). It was decided to evaluate staged risk assessment using a risk score followed by glucose testing where appropriate. We refer to such combined approaches as risk assessment strategies.

The advantages of including a risk score stage are:

- this is a cheap way of reducing the number of individuals that need to undertake invasive glucose testing and those at very low risk of diabetes
- it reduces the cost per case detected
- capacity within primary care is unlikely to exist to perform blood tests on everyone

For each risk score option, there are alternative cut-points or thresholds above which an individual proceeds to the next stage of risk assessment (i.e. glucose testing). Similarly, a range of cut-points can be applied to glucose (FPG or HbA1c) test results to separate individuals with NGT and IGR. There would therefore be a very large, unmanageable number of permutations of risk score tools, glucose tests and associated cut-points to evaluate. The following process has therefore been followed to reduce down the number of options:

i)   identify the most suitable risk scores (see Section 2.2.4.2 below)
ii)   agree on the most suitable glucose tests (see Section 2.2.4.3 below)
iii)   define and apply criteria for appropriate possible cut-points for risk scores and IGR (see Section 2.2.4.4 below)
iv)   assess performance and calculate the cost-per-case detected of the alternative risk assessment strategies (see Results Section)
v)   from iv), identify the most likely cost-effective and feasible strategies for full economic evaluation (i.e. by assessing the overall long-term costs and benefits)

2.2.4.2 Risk scores chosen

The Vascular Checks algorithm includes an initial assessment stage using a combination of blood pressure and BMI as criteria for further testing.

For the other strategies, alternative risk scores for undiagnosed diabetes and IGR were considered (scores that only covers symptomatically or clinically detected diabetes were not considered appropriate for this purpose). The Leicester Practice Risk Score (LPDS) [30] and Leicester Self Assessment Score [29] have been chosen rather than the Cambridge Diabetes Risk score [28] because these include ethnicity which is an important determinant of the risk of diabetes.

There are pros and cons to choosing between the Leicester Self Assessment (LSA) Score and the Leicester Practice Risk Score (LPDS) which uses GP-based medical records. The latter is cheaper and automated but requires completeness of the required risk factor data (gender, ethnicity, BMI, family history of diabetes, use of antihypertensive medication). Participation of patients in the process of completing questionnaires and recording their risk factors may itself act as a form of brief intervention. As these tools have similar diagnostic performance, the negligible cost of the LPDS is likely to make it preferable to the LSA Score for those patients who have the requisite data held in GP databases.

Ultimately, local flexibility will be needed regarding use of the practice records based LPDS versus the self-assessment tool (LSA), e.g. taking into account the quality and completeness of GP medical records.

We have not modelled the criteria laid down by the IMAGE group. These are but these are similar to those included in the Leicester and Cambridge risk scores so are likely to have similar performance characteristics.

<u>South Asians aged 25-39</u>

After the completion of the modelling, the PDG discussed using a BMI cut-off of 23 (rather than a risk score that hadn't been calibrated to this age group) as a means of identifying individuals that should have a glucose test. Although too late to do a full evaluation of this, the impact on the number proceeding to glucose testing and number of cases of undiagnosed IGR and diabetes are shown in Appendix 3.

2.2.4.3 Glucose tests chosen

Given time constraints, in order to limit modelling options to a feasible number, we have evaluated FPG and HbA1c tests but not –

- FPG and HbA1c in combination
- OGTT (which is considered unacceptable to many patients)
- random glucose testing (as this was unlikely to feature much in future practice)
- the 1-hour Glucose Challenge Test (GCT)

2.2.4.4 Preliminary set of risk assessment strategies

A test or risk assessment strategy does not have a single sensitivity etc. There is a range depending on cut-points chosen, i.e. the threshold above which the result is deemed to be positive. In theory, it would be possible to evaluate numerous alternative cut-points to find the optimal one. In practice, the number of options evaluated may be constrained by practical issues such as the cut-points for which performance data is available, and acceptability issues – for example, a desirable target for the minimum proportion of undiagnosed cases.

In line with some preliminary cost-per-case detected analyses undertaken by the research team in Leicester, we were advised to aim for a sensitivity for Type 2 diabetes of close to 80%, on the grounds that a reasonable objective of risk assessment is to make sure that at least 80% of cases of undiagnosed diabetes are detected.

It was also assumed, in agreement with the PDG, that the cut-point for the risk score stage should exclude at least 20% of individuals from proceeding to glucose testing given practical constraints on the number of glucose tests that could reasonably be carried out within primary care. Shown in Table 4 below are the resulting set of permutations for the risk score stage and glucose testing for which to calculate the sensitivity and cost-per-case detected. .

The last strategy in Table 4 may be considered the base case because this is the approach currently recommended within the NHS Vascular Checks Program in Primary Care in the UK. Although this may now be less desirable because of the inclusion of an OGTT, it is necessary to demonstrate whether alternatives are more cost-effective using the modelling, taking account of factors such as the cost and lower uptake of OGTTs compared to HbA1c and FPG tests (see Section 2.2.7).

2.2.5 Measuring performance of alternative algorithms

Performance of risk assessment algorithms is usually measured in terms of sensitivity, specificity and positive predictive value (these terms are defined fully in Appendix 4). There is usually a trade-off between sensitivity and specificity, which can be represented using Receiver Operating Characteristic (ROC) curves.

However, where the same glucose test is used as that for defining diabetes and IGR, specificity is always 100% (i.e. there can be no 'false positives'). Sensitivity (the proportion of cases of IGR/diabetes detected) is almost certain to be lower than 100% when a risk score is used prior to glucose testing (because the risk score may falsely rule out some patients with IGR or diabetes).

In addition to sensitivity, we will also report –

- cost per case detected
- number of blood tests
- % of cases of diabetes and IGR detected

2.2.6 LEADER dataset

The Leicester Ethnic Atherosclerosis and Diabetes Risk (LEADER) Study was designed to identify the prevalence of undiagnosed T2DM and the characteristics of those individuals found to have screen-detected T2DM and this dataset has been used to estimate the performance of the different risk assessment strategies.

This screening study was conducted in Leicestershire with a population of over 950,000 in the relevant age-range, approximately one third of whom are resident in the City of Leicester (30% of whom class themselves as belonging to Indian, Pakistani or Bangladeshi ethnic groups on the 2001 census). The LEADER cohort is a combination of two systematic screening programmes and different strategies were used for participant selection in each study. Approximately two-thirds were screened regardless of risk for T2DM. The remaining approximate one-third was selected for having a risk factor for T2DM, as recommended by Diabetes UK. Participants were recruited from 40 Leicestershire general practices (high and low deprived areas). All individuals aged 40-75 years, and additionally those aged 25-39 years if not of white European origin, were invited to attend for screening and an OGTT was carried out according to WHO 1999 criteria [31]. Simultaneously an HbA1c measurement was taken and measured on a correctly aligned assay analyser. The screening was conducted in general practice, a mobile screening unit, or at one of the Leicester teaching hospitals, between February 2002 and August 2009. Those identified by the programme with IGR are offered an annual follow up. As of 2011, 9494 people have been screened and have a complete dataset on the LEADER database. The dataset includes HbA1c, FPG, OGTT, FINDRISC and routine demographics collected on all patients with Type 2 diabetes.

2.2.6.1 Baseline characteristics

The mean age of the cohort was 55.7 years; 52.2% were female. Regarding ethnicity, 68.1% were of white European origin and 27.0% were south Asian (leaving 4.9% from other ethnic backgrounds including mixed racial backgrounds). As there is appropriate representation of south Asian groups, our data apply to the UK and much of northern Europe. Using WHO 1999 criteria [31], 3.3% were diagnosed as having T2DM, with a higher prevalence in south Asians compared to white Europeans (4.9% vs. 2.9% respectively); 5.2% had an HbA1c ≥6.5%. A further 15.0% were detected as having IGR (Impaired Glucose Tolerance or Impaired Fasting Glycaemia).

Table 4 : Preliminary Set of Risk assessment strategies to be evaluated

Risk score & cut-point	Glucose test and cut-point for IGR	Third stage
LSA ≥ 10 points	HbA1c ≥ 5.7%	N/A
LSA ≥ 13 points	HbA1c ≥ 5.7%	N/A
LSA ≥ 16 points	HbA1c ≥ 5.7%	N/A
LSA ≥ 10 points	HbA1c ≥ 5.85%	N/A
LSA ≥ 13 points	HbA1c ≥ 5.85%	N/A
LSA ≥ 16 points	HbA1c ≥ 5.85%	N/A
LSA ≥ 10 points	HbA1c ≥ 6.0%	N/A
LSA ≥ 13 points	HbA1c ≥ 6.0%	N/A
LSA ≥ 16 points	HbA1c ≥ 6.0%	N/A
LPDS ≥ 4.75	HbA1c ≥ 5.7%	N/A
LPDS ≥ 5.0	HbA1c ≥ 5.7%	N/A
LPDS ≥ 5.25	HbA1c ≥ 5.7%	N/A
LPDS ≥ 4.75	HbA1c ≥ 5.85%	N/A
LPDS ≥ 5.0	HbA1c ≥ 5.85%	N/A
LPDS ≥ 5.25	HbA1c ≥ 5.85%	N/A
LPDS ≥ 4.75	HbA1c ≥ 6.0%	N/A
LPDS ≥ 5.0	HbA1c ≥ 6.0%	N/A
LPDS ≥ 5.25	HbA1c ≥ 6.0%	N/A
LSA ≥ 10 points	FPG ≥ 5.5 mmol/L	N/A
LSA ≥ 13 points	FPG ≥ 5.5 mmol/L	N/A
LSA ≥ 16 points	FPG ≥ 5.5 mmol/L	N/A
LSA ≥ 10 points	FPG ≥ 5.7 mmol/L	N/A
LSA ≥ 13 points	FPG ≥ 5.7 mmol/L	N/A
LSA ≥ 16 points	FPG ≥ 5.7 mmol/L	N/A
LSA ≥ 10 points	FPG ≥ 6.0 mmol/L	N/A
LSA ≥ 13 points	FPG ≥ 6.0 mmol/L	N/A
LSA ≥ 16 points	FPG ≥ 6.0 mmol/L	N/A
LPDS ≥ 4.75	FPG ≥ 5.5 mmol/L	N/A
LPDS ≥ 5.0	FPG ≥ 5.5 mmol/L	N/A
LPDS ≥ 5.25	FPG ≥ 5.5 mmol/L	N/A
LPDS ≥ 4.75	FPG ≥ 5.7 mmol/L	N/A
LPDS ≥ 5.0	FPG ≥ 5.7 mmol/L	N/A
LPDS ≥ 5.25	FPG ≥ 5.7 mmol/L	N/A
LPDS ≥ 4.75	FPG ≥ 6.0 mmol/L	N/A
LPDS ≥ 5.0	FPG ≥ 6.0 mmol/L	N/A
LPDS ≥ 5.25	FPG ≥ 6.0 mmol/L	N/A
Vascular Checks Algorithm : BMI≥30 (or 27.5 for South Asians) or HxHT or BP ≥140/90	FPG ≥ 6 mmol/L	OGTT (WHO criteria for diabetes)

2.2.6.2 Analysis of performance using LEADER dataset

The LEADER dataset contains the LPDS risk score (latest modified 'Score 3'), risk factors to enable calculation of the LSA score, an FPG and an HbA1c test. As two test results are needed to diagnose diabetes, assumptions were necessary in order to determine how many cases of diabetes would be identified through risk assessment:

- If the 1st FPG is greater than or equal to 7.0 mmol/L, then a randomly sampled 2nd FPG result (Yes/No ≥ 7 mmol/L) is drawn on an individual basis based on knowledge of the proportion of initial results ≥ 7 than are followed by a second result ≥7. Records from a subset of the LEADER study where 2 FPG tests were undertaken suggest that approximately 70% of repeat FPG tests confirm diabetes (i.e. FPG ≥7).

- For HbA1c testing, for the purpose of determining the outcome of risk assessment, we assumed that the result of the 1st test would not be changed by the confirmatory test. This is a reasonable assumption because HbA1c is much more repeatable than FPG, with a much lower variation between consecutive test results. We have, however, included the cost of a 2nd confirmatory HbA1c test where the initial test indicates diabetes as this is required for a formal diagnosis of diabetes.

The PDG advised that local implementation of separate algorithms for BMEs would be confusing, and not practical so we have not analysed separate algorithms for this subgroup.

2.2.7 Unit Costs and Uptake of Risk Scores and Glucose Testing

In

Table 5 below, the costs of risk scoring and testing include administration, staff and laboratory costs, as well as the direct cost of any test itself.

The cost of the LPDS is very low because this would just involve setting up a prompt within the GP computer system that a diabetes test is recommended when a patient next visits their GP (for whatever reason).

The uptake rates shown are based on rates reported in Evidence Statement 18 of Review 1 (although reporting of uptake rates was patchy), and advice from the PDG. Given the uncertainty, sensitivity analyses were undertaken.

A necessary assumption for the modelling is that those that take up risk assessment are at similar risk of diabetes to those that do not. This may not be true and may lead to some overestimation of the benefits of risk assessment but is unlikely to affect the relative cost-effectiveness of alternative risk assessment strategies.

A minority of the population present to their GP for (confirmatory) glucose testing via a community-based risk assessment facility (e.g. a pharmacy), having possibly had an initial glucose test. The cost to the NHS of risk assessment might be slightly different for such individuals.

Table 5 : Assumed Unit Costs and Uptake Rates of specific components of risk assessment strategy

Test	2011 Cost	Source	Uptake assumption
LPDS (Risk score)	£ 0.24	Personal communication, Kamlesh Khunti.	95% (assumed to have complete data on risk factors within LPDS)
LSA (Risk Score)	£ 5.28	Vascular Checks modelling Consultation [32] (Table 3)	50%
Fasting Plasma Glucose	£ 11.50	Vascular Checks modelling Consultation [32] (Table 3)	70% (90% for confirmatory)
HbA1c	£ 14.00	Estimate based on difference in laboratory costs from FPG (Personal communication, Kamlesh Khunti)	80% (90% for confirmatory)
OGTT	£ 23.94	Vascular Checks modelling Consultation [32] (Table 3)	80% when used as a confirmatory test

The specific cost components are shown Table 6 below.

2.2.8 Issues for consideration on risk assessment strategies

2.2.8.1 Caveats around Hba1-based risk assessment

The generalisability of results from one study to the rest of UK was raised during a PDG meeting. The mean HbA1c of a population is an important determinant of the performance (e.g. sensitivity) of a risk assessment strategy. In the population-based LEADER screening study within Leicestershire, the mean HbA1c value was 5.7% [25] but was only 5.1% in the Whitehall II study [33] and was also lower in the EPIC study.

The evidence for prevention of diabetes in patients identified with IGR using an HbA1c test is weak (compared to that for OGTT-defined IGR) so the degree of success in preventing diabetes in such individuals is less certain.

Evidence for how response to intervention for IGR, and ultimately prevention of diabetes, varies according to baseline HbA1c is also limited. Any emergence of better evidence could significantly alter which HbA1c bracket is considered the priority for intervention.

Ideally, a multivariate risk tool is needed that shows the relative contributions of fasting plasma glucose, HbA1c and risk factors to the prediction of future events. Should this become available, it would be possible to choose a cut-point on some new multivariate algorithm such that the same proportion of individuals are treated to reduce risk of diabetes as that determined by our analyses. This would provide a reasonable

degree of assurance that treatment of individuals identified by such an algorithm is cost-effective. An analysis by Bonora et al [34] shows that HbA1c is predictive after adjustment for typical risk factors used in risk scores, so the dataset from this study could potentially support the development of a multivariate risk tool.

Table 6 : Costs of tests

Test	Admin	HCA / nurse Time	Lab costs	Full Cost	Year	Inflation uplift to 2011 rates	2011 Cost
Leicester Self Assessment	£ 4.70			£ 4.70 [32]	2006	1.124	£ 5.28
Fasting Plasma Glucose		£ 4.13	£ 6.10	£ 10.23 [32]	2006	1.124	£ 11.50
HBA1c test							£ 14.00
Oral Glucose Tolerance Test (OGTT)		£ 9.00	£ 12.30	£ 21.30 [32;32]	2006	1.124	£ 23.94

The inflation uplifts are derived and estimated from Curtis 2010 (as per set out in

Appendix 5).

2.2.8.2 Caveats around FPG-based risk assessment

The evidence for prevention of diabetes in patients identified with IGR using an FPG test is weak so the degree of success in preventing diabetes in such individuals is less certain. Specifically, the Early Diabetes Intervention Trial suggested the effectiveness of pharmacologic therapy in those with IFG might be lower than in those with IGT [35]. It has been suggested than an FPG >=6 may be an appropriate threshold for IGR but this would identify a group with a higher FPG than those in the Finnish DPS and US-DPP prevention trials. The response to intervention at such higher baseline FPG levels is less certain.

2.2.8.3 Caveats around using an arbitrary glucose cut-point

It is recognised that an arbitrary glucose cut-point to determine those at high risk of diabetes warranting intervention is not ideal. However, the use of a risk score in the proposed risk assessment algorithms will ensure to some degree that those with a low risk score are not treated, regardless of their glucose level.

There may be concern that some individuals may not receive intervention despite having a high risk score. It should not however be assumed that an individual with a high score, <u>but a glucose level below the threshold</u> for intervention, is at as high risk as the average risk of <u>all</u> individuals with that score. Nevertheless, patients with a risk score above a certain cut-point could be recalled for regularly monitoring regardless of their HbA1c or FPG. There is a need for a multivariate equation for undiagnosed IGR and diabetes that simultaneously takes account of risk factors and glucose levels, this being of particular value for those with a high risk score but a low to moderate glucose level.

2.3 <u>Possible outcomes of risk assessment and subsequent treatment pathways</u>

Below are the treatment pathways that we have assumed according to actual glucose status at risk assessment, the result of risk assessment, and uptake or otherwise of preventive intervention for individuals 'diagnosed' with IGR. The proportional split figures provided in the end column are for illustration only.

2.3.1 Risk assessment Outcomes of Interest

As well as the cost-per-case detected, other considerations which will influence commissioners are –

1) What will it cost commissioners in up-front investment to implement interventions?
2) How many blood tests would this involve?
3) How does increasing the amount of investment and choice of risk assessment strategy affect the number of cases of diabetes that can be delayed/prevented?

Table 7 : Outcomes of risk assessment and subsequent treatment pathways

| Actual status | Risk assessment outcomes | Proportion of Actual Cases with True/False test result | <-------------- Treatment Pathway --------------- > | | |
			Recommended (based on test)	Actual (adj for uptake of intervention)	Proportion
Diabetes	Diabetes (TP)	95%	Diagnosed T2DM	Diagnosed T2DM	95%
	NGT (FN)	5%	No treatment	Undiagnosed diabetes	5%
IGR	IGR (TP)	89%	Treated IGR	Treated IGR	53%
			Treated IGR	Untreated IGR (non-uptake))	36%
	NGT (FN)	11%	No treatment	Untreated IGR	11%
NGT	NGT (TN)	100%	No treatment	No treatment (NGT)	100%

FN = False Negative, TN = True Negative, TP = True Positive

For individuals with undiagnosed IGR, we assume that rates of subsequent detection of IGR are negligible in the absence of repeat testing.

2.3.2 Baseline diabetes-related co-morbidities

We have assumed no complications at baseline amongst those screened because:

- we assume that there would be no one with undiagnosed diabetes or IGR and prevalent CVD because people with CVD should automatically be screened for diabetes and IGR as part of (CVD) secondary prevention
- the baseline prevalence of microvascular complication is assumed to be 4.6%, 1.8% and 0.2% for retinopathy, microalbuminuria and macroalbuminuria respectively amongst patients with diabetes (Waugh et al 2005) and nil for patients with IGR.

2.4 Natural History of NGT, IGR and Undiagnosed Type 2 diabetes

2.4.1 Progression from IGR to Type 2 diabetes

We have based progression on the control arm of the Finnish Diabetes Prevention Study (DPS) in which 38% had developed diabetes after 6 years [36]. As this was an RCT, progression rates would be expected to be higher than the rate that would be observed in an epidemiological study. Different rates may be particularly due to –

- different levels of baseline risk of diabetes – the Finnish Study represented a high-risk group, although use of a risk score followed by a glucose test may also identify a relatively high risk group
- the presence of basic advice and regular monitoring which has the effect of a low intensity intervention

The control arm of the DPS resulted in a weight loss of 1 kg sustained to year 4 so we assume that this resulted in a 16% reduction in risk (based on the estimate per Hamman 2006 [37]) – we use this to scale down the DPS rates to obtain progression rates in a cohort with undiagnosed IGR.

For the economic modelling, an individual's progress (or otherwise) from IGR was determined, and where applicable, the time point at which they develop diabetes. This allows individual trajectories of glycaemic progression to be modelled correctly, i.e. with a non-linear increase in HbA1c rather than a linear change.

2.4.2 Progression from NGT to Diabetes

As a result of being below rather than above the arbitrary glucose cut-point for IGR for a particular risk assessment algorithm, some individuals will not receive an intervention despite having a high risk score for undiagnosed diabetes or IGR. In practice, the choice of initial risk assessment strategy is not considered to have a significant impact on the long-term outcome of such individuals with NGT as they should be detected at the next risk assessment visit (although the model does not include repeat testing). Most individuals, probably around 80%, in the Vascular Checks program have at least one risk factor for CVD or Chronic Kidney Disease (CKD) that would lead to an annual check. Even if the remainder were not re-checked until 5 years later, this would result in an average of 2 years between testing for this subgroup as a whole.

The consequences for the current modelling exercise are considered to be negligible. Although a minority of individuals might progress from NGT to diabetes within 2 years – this rate is estimated to be very low, approximately 0.5% p.a. based on the FIN-D2D study and other study results discussed in the same publication [38] (the rate was 2.0% and 1.2% in men and women in FIN-D2D, which was between twofold and six fold higher than that in some previous studies). This would mean a cumulative incidence of around 1% over a 2-year period amongst the approximate 85% of individuals with NGT at baseline. This is very small compared to the lifetime incidence of the order of 70% amongst the 15% of individuals with IGR at baseline

Moreover, the majority of individuals with relatively normal glucose levels would have the same risk assessment outcome and long-term clinical outcomes regardless on the specific risk assessment strategy. For this reason, we have not modelled progression from NGT to IGR or diabetes.

This is not to say that these individuals at relatively low risk could not be offered appropriate advice about the benefits of lifestyle changes. In the Baltimore Longitudinal Study of Aging [39], over a mean follow-up of 11.4 years, 279 of 488 patients progressed from NGT to IGR, i.e. 57%. This is equivalent to 5% p.a. The mean age at baseline was 53, 25% had one or more 1st degree relatives with diabetes and 26% were over 65 years of age. Some patients were followed up for up to 20 years and results suggest that at least 70% of such a population progress to IGR over 20 years. This highlights that even those at low (average) risk of diabetes should maintain a healthy weight, diet and levels of physical activity.

2.4.3 Undiagnosed Type 2 diabetes and subsequent detection

With the risk assessment algorithms proposed in Table 4 above, most remaining cases of undiagnosed diabetes would be due to non-attendance for risk assessment rather than fallibility of the risk assessment method, so it is debatable at what point such patients would be subsequently detected opportunistically. In the DESMOND study of newly-diagnosed patients, the mean HbA1c at baseline (soon after diagnosis) was 8.1% [40]. We have previously estimated HbA1c for screen- detected diabetes to be around 6.4% [3]. HbA1c progression between these two HbA1c levels is modelled as an increasing non-linear trajectory.

2.5 Interventions to prevent or delay progression from IGR to diabetes

2.5.1 Prevention or delay?

It is arguable to what extent long-term prevention of diabetes is likely to be attainable in the real-world. Analyses from the Finnish DPS [21] and EPIC-Norfolk cohort [22] have shown that individuals that achieve a set of lifestyle goals have very little if any risk of diabetes over an average duration of 4 to 5 years. However, pragmatic interventions are likely to be less intensive and may have a lower effectiveness than those in clinical trials. In addition, over the long-term, some individuals are unlikely to be able to sustain such lifestyle behaviours and so may delay but not prevent the onset of diabetes (although it should be remembered that not all individuals with IGR would progress to diabetes even without any lifestyle change).

2.5.2 RCT evidence

Large RCTs have consistently shown that diabetes can be delayed or prevented, with a reduction in incidence of diabetes of 43% [36] and 34% [41] at 8 and 10 years respectively with lifestyle intervention. It should be remembered that subjects in trials of intensive lifestyle modification were highly selected. For example, smoking prevalence was only 7%. The same gains from lifestyle intervention are therefore unlikely to be seen in the real world [42].

2.5.3 Cost Elements of Intervention in Finnish Diabetes Prevention Study

The costs per annum shown below are based on resource use reported in an economic analysis of the DPS intervention in a Swedish setting [43]. These are separate for the first and subsequent years and are shown below.

Table 8: Breakdown of Finnish DPS intervention costs

Component of intervention	Unit Cost - Sweden	First Year		Subsequent	
		Resource	Costs	Resource	Costs
Direct Costs					
visits to the physician	€ 73	1	€ 73	1	€ 73
visits to the nutritionists	€ 39	7	€ 273	4	€ 156
participation in 2 circuit-type resistance training sessions per week – each estimated to cost €818 (per year) for a group of fifteen persons - assumes a mean participation rate of 67.5 percent	€ 37	2	€ 74	2	€ 74
Indirect Costs					
costs associated with time and travel to physicians	€ 38	8	€ 304	5	€ 190
Total Direct Cost			€ 724		€ 493

This shows that visits to a professional dietitian were the largest cost component. Given this and the limited capacity of NHS dietitians, some training of other healthcare or local authority staff groups may help to deliver cost-effective real-world adaptations of the intervention in the Finnish DPS and US DPP.

2.5.4 Evidence for the effectiveness of pragmatic lifestyle interventions

2.5.4.1 Lifestyle intervention – initial effectiveness

The interventions identified in Review 3 generally show a strong relationship between financial costs per participant and average weight loss achieved. These translation studies are often more efficient in terms of weight loss achieved per unit cost than the large DPS and DPP RCTs, as they generally take place in a group rather than 1-to-1 setting without proportional loss of efficacy. One of the studies in review 3 (Kramer 2009) reported 2 hours preparation time to deliver a education session (similar to one of the 16 session in the US Diabetes Prevention Program) that lasts for 1 hour. However for experienced trainers delivering frequent courses, we have assumed that 1 hour's staff preparation time per course is sufficient. Other costs apart from delivering courses (e.g. admin, materials) have been taken account of separately.

Figure 2 below shows the weight loss and estimated cost for the various interventions in Review 3.

Figure 2 : Cost versus weight loss achieved

kg loss vs cost
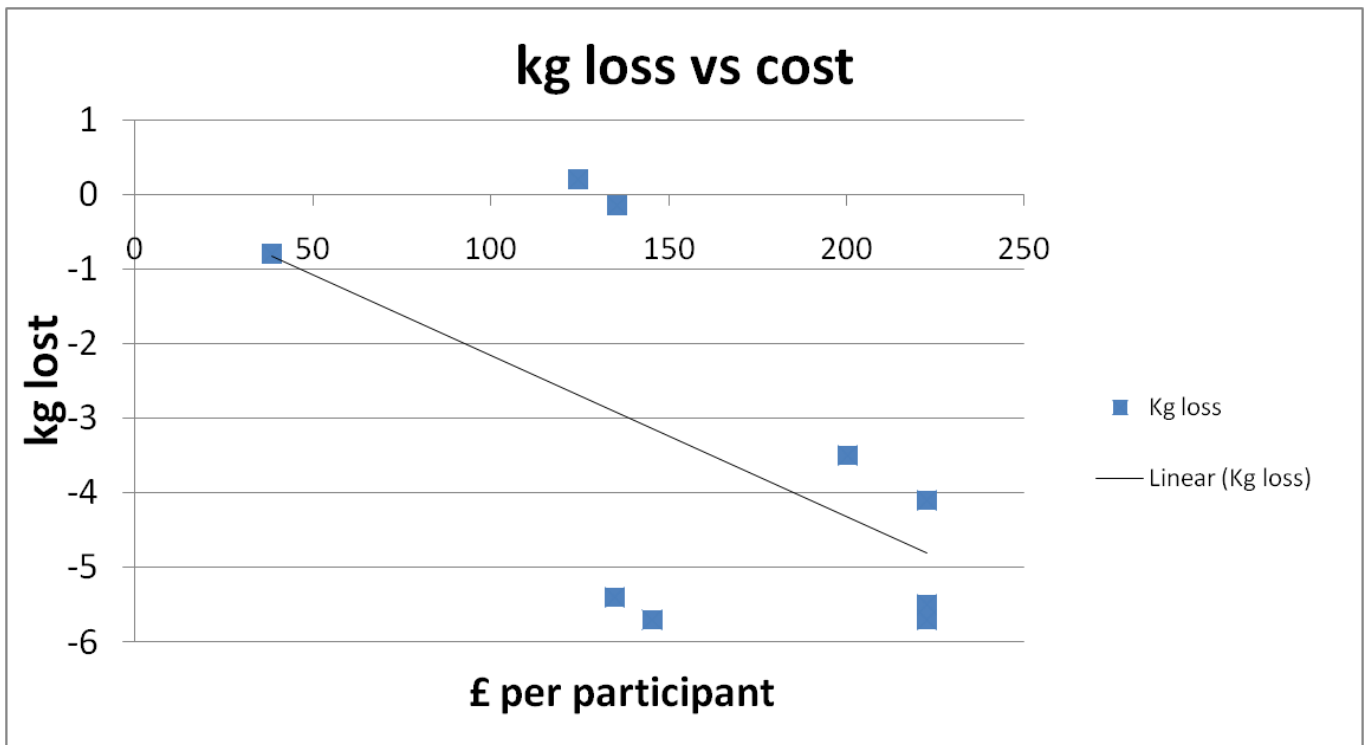
The costings include :

- Costs relating of courses : staff costs, course materials, food models, venue hire
- Cost of training educators
- Quality assurance of educators
- Booking patients onto course, sending letters, booking rooms etc
- An uplift rate of 22% on all of the above costs to cover general overheads (e.g. estate costs, central admin and management department costs)

Although most studies only report on the staff involved in the delivery of courses, we have included estimates for the other cost elements based on our experience of costing the DESMOND intervention [40]. The economics subgroup had a mixed view on the maximum group size of classes – currently 8-10 is standard practice for many NHS lifestyle-related courses in the UK but many of the DPP translation studies had 15-17 and achieved good results. The Norfolk Diabetes Prevention Study has a group size of 10-12 participants [44]. Related to this issue are the number of educators required, and their level of experience.

Some studies were before and after studies, whilst in others, it was not clear whether their results were on an ITT basis or for completers only. Some results may therefore be optimistic in terms of what can be achieved in practice. Conversely, through ongoing learning about best practice for delivering lifestyle prevention programmes, there may be opportunities to improve their efficiency. For example inclusion of pedometers would be considered good practice – we added £ 10 to the intervention cost to cover this.

We have modelled the following intervention scenarios with the effects during the first year and associated costs shown in Table 9 below. These represent a level of effectiveness between the average effectiveness of the studies and the optimal studies in review 3.

Table 9 : Initial Weight loss scenarios

	Assuming sub-optimal adherence

Scenario	Weight loss (kg)	Cost - year 1 (£)	Associated SBP reduction (mmHg)
Scenario WL1 (low intensity)	1.5	50	1.5
Scenario WL2 (moderate intensity)	3.0	100	3.0
Scenario WL3 (intensive)	4.5	150	4.5

The reduction in systolic blood pressure is based on an approximate 1:1 association between weight loss and SBP in the Finnish DPS.

In addition to the intervention cost, we assume an annual HbA1c test costing £ 14 for monitoring patients with diagnosed IGR, and an appointment with a nurse costing £ 12 (Curtis 2010 [45], Section 10.6) to discuss the results and re-enforce lifestyle change.

Limitations of evidence for real world effectiveness

Translational studies based around the DPP often lacked control arms. One study, carried out by Almeida [46] that had the largest sample (n = 1,520), longer follow up (12 months) and a control arm, reported a mean body weight loss 0.8kg greater in the intervention arm than controls (1.6 kg vs. 0.8 kg).

2.5.5 Evidence for long term impacts of RCT interventions

Long-term follow-up of prevention studies in Finland and America show that there is a gradual regain of weight on average. The absolute reduction in risk seems to be maintained over time but the relative risk reduction reduces once the period of active intervention ends (after 4 years in the Finnish and American studies).

For lifestyle intervention, effectiveness reported in long-term follow-up studies may underestimate the effect of intervention because controls may have taken up healthy behaviours having seen the 4-year results, i.e. there may be contamination between study arms.

2.5.5.1 Weight maintenance - scenarios

A 1-year intervention without subsequent sessions to re-enforce knowledge of self management is likely to be inadequate in sustaining behaviour change. The large diabetes prevention trials and two implementation studies (in particular Vadheim 2010) suggest that after-core sessions can be effective in maintaining weight loss. In Vadheim, these were 6-monthly sessions and people attended an average of 3.9 of these. We have modelled the following maintenance intervention scenarios.

The trajectories of weight regain for the above scenarios are shown in Figure 3 below.

Table 10 : Weight maintenance scenarios

Maintenance scenarios	£ Per patient per session	Total maintenance cost	Effect
A. annual after-core session for years 2 to 4 (at start of year)	£20	£60	weight regain delayed such that av. weight loss nil by end of year 4
B. 6-monthly after-core session for years 2 to 4	£20	£120	weight regain delayed such that av. weight loss nil by end of year 6
C. after-core sessions every 4 months for years 2 to 4	£20	£180	weight regain delayed such that av. weight loss nil by end of year 8

Figure 3 : Trajectories of weight regain for each maintenance scenario (for an assumed initial loss of 3kg)
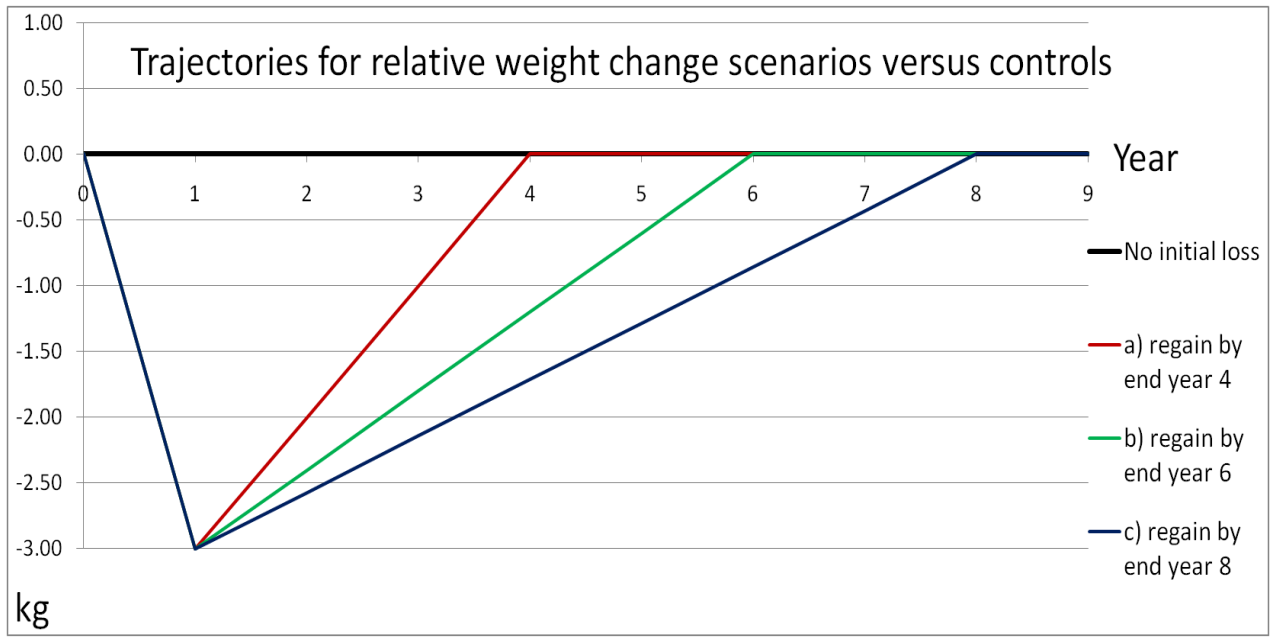
In addition, we assume an annual HbA1c test costing £ 14 for monitoring patients with diagnosed IGR, and an appointment with a nurse costing £ 12 (Curtis. PSSRU 2010 [*]) to discuss the results and re-enforce lifestyle change.

2.5.6 Modelling the effects of Weight loss and Physical Activity on risk of diabetes

For interventions that have an effect of reducing weight, the effect on risk of diabetes is modelled using the relationship reported in Hamman (16% reduction in risk per kg of weight loss [37]). However, some interventions may increase physical activity in some individuals without significant associated weight loss. Evidence from RCTs shows that it is still possible to achieve a large reduction in risk of diabetes through increases in physical activity, even in the absence of weight loss [47, 37]. Ultimately, the PDG advised that the

---

[*] Section 10.6

most appropriate interventions to model should target weight loss or maintenance as well as physical activity, although it was recognised that interventions primarily aiming to increase physical activity may be suitable for some individuals.

2.5.6.1 Benefits after intervention has stopped

The follow-up of the Finnish DPS showed that some of the benefits, accrued at the point at which active intervention stopped, are maintained longer-term. However, as shown by the increases in relative risk for diabetes for the intervention versus control arm, there is some loss of effect which is in part likely due to at least partial regain of weight amongst many participants. In fact, up to 10 years following the start of intervention, the average weight loss appears to be a good predictor of the reduction in incidence of diabetes.

There is some evidence from the 20-year Chinese Da Qing study that improved insulin sensitivity has some ongoing benefit in reducing incidence of diabetes, even once net weight loss (versus controls) has been regained [48].

Any such independent effect is difficult to identify and quantify across the 4 large prevention trials (DPS, US-DPP, Indian-DPP, Da Qing) so we have conservatively not assumed any such effect in the modelling.

2.5.7 Effectiveness of Interventions in Cohorts with IGR identified by HbA1c or FPG

There are some doubts as to whether the degree of benefit observed in the large diabetes prevention trials would be replicated in cohorts identified with IGR through HbA1c or FPG-based risk assessment (even with the same intensity of preventive intervention). These doubts are two-fold, relating to the baseline level of glucose and the ability to reduce risk of progression when there is a relatively greater abnormality of fasting glucose rather than 2-hour glucose.

2.5.7.1 Evidence for prevention in patients identified by FPG

Evidence for prevention in patients identified by FPG is lacking and the Early Diabetes Intervention Trial (EDIT) suggested that the ability of therapies to reduce risk of diabetes may differ for those with IGT or IFG [35]. Depending on the cut-point used, compared to an OGTT, this test tends to identify a greater proportion of individuals with Impaired Fasting Glucose (IFG), of which some also have Impaired Glucose Tolerance (IGT). The best evidence for prevention comes from studies of patients with IGT in which interventions primarily reduce 2 hour glucose rather than fasting glucose levels.

As most of the evidence for effectiveness comes from studies of individuals with IGT, there are some doubts about effectiveness in terms of reduction in incidence of diabetes in individuals that have been identified with IGR using an HbA1c or FPG test. This is particularly so for FPG, as fasting glucose is more difficult to lower whereas there is a notable reduction in 2 hour glucose through lifestyle intervention as shown in Figure 4 below.

Furthermore, depending on the FPG cut-point used, average FPG levels may be higher than those in the Finnish DPS and US DPP (average baseline FPG 5.9 -6.1 mmol/L), which would translate into a higher baseline risk of diabetes as shown by in Figure 5 below, and evidence for the effectiveness of prevention from relatively high baseline FPG levels is lacking.

Figure 4 : Reduction in fasting and 2-hour plasma glucose, and HbA1c levels with intervention
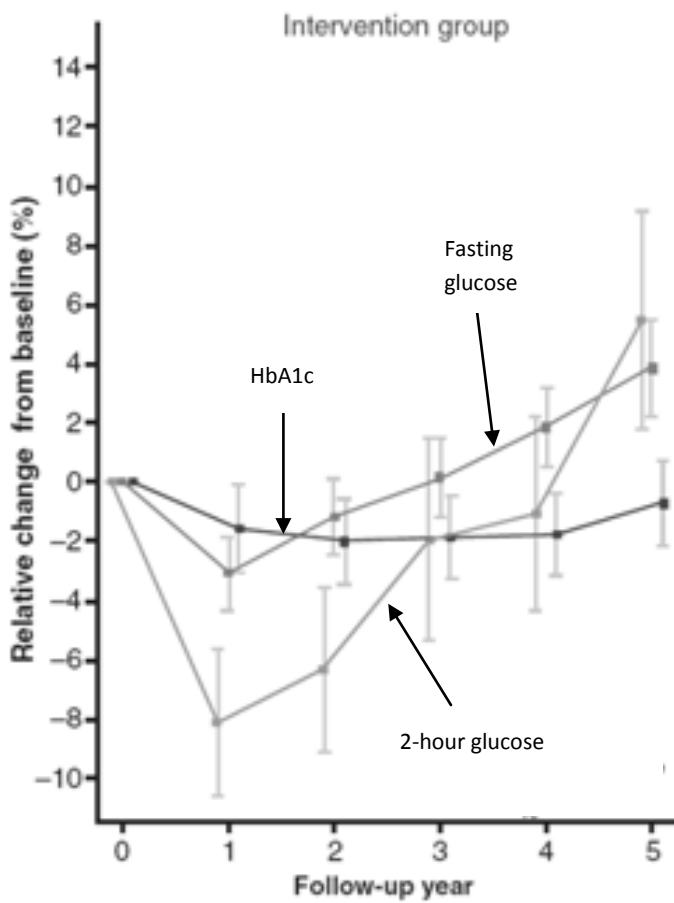
(Figure reproduced with permission from Pajunen et al. Diabetic Medicine 2011 [49])

Figure 5 : Incidence of diabetes according to baseline FPG
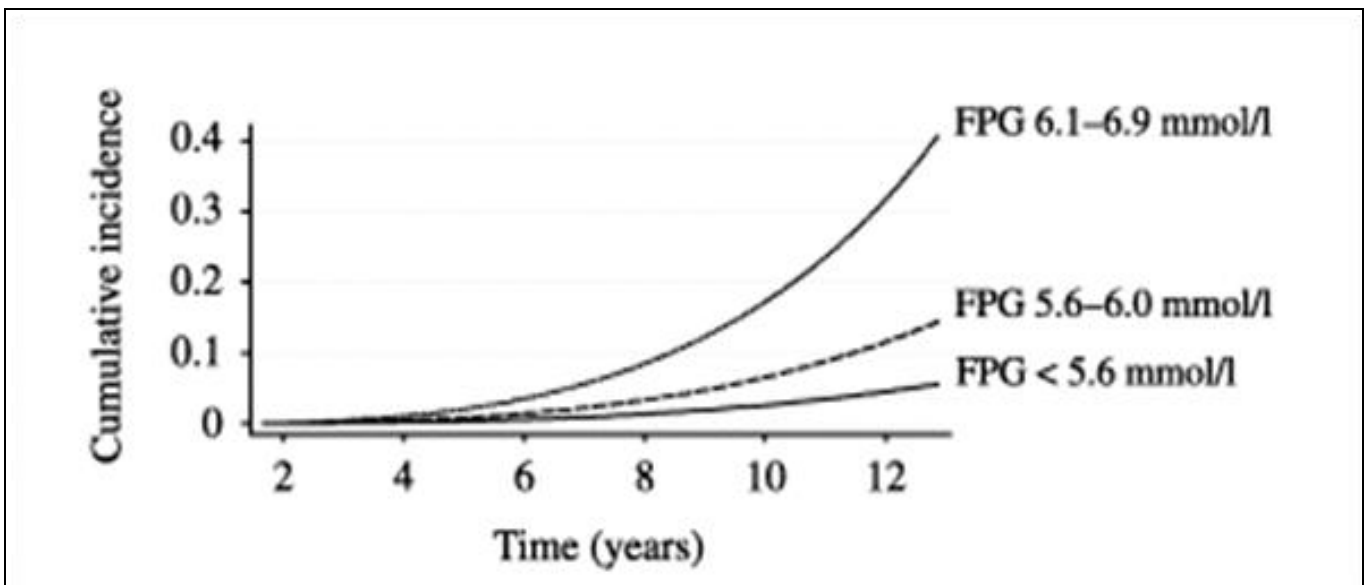
(Figure reproduced with permission from Forouhi et al. Diabetic Medicine 2007 [50])

2.5.7.2 <u>Evidence of prevention in HbA1c-identified cohorts</u>

Similarly, depending on the HbA1c cut-point used, average HbA1c levels may be higher than in the Finnish DPS and US DPP (average baseline HbA1c 5.65%- 5.9% in the DPP and DPS), and evidence for the effectiveness of prevention from relatively high baseline FPG levels is lacking.

We have been unable to reliably compare the relative FPG and 2-hour glucose distributions of individuals identified with IGR using FPG and HbA1c tests. This would be useful as it would enable comparison with the distribution of glucose amongst individuals identified using an OGTT.

2.5.7.3 Scenarios for effectiveness of preventive interventions

Given concerns amongst PDG members about the above uncertainty, we conservatively assumed interventions in those identified with IGR through FPG or HbA1c tests achieve 70% of the effectiveness of intervention in individuals with IGT (not necessarily isolated IGT).

Although the effectiveness scenarios are the same for FPG and HbA1c-screened cohorts, there is a lack of evidence around this. Notably, in the LEADER dataset, using an HbA1c cut-point of 5.7% gives a higher mean HbA1c than the Finnish Diabetes Prevention Study but both lower FPG and 2 hour glucose. This may be due to the storage of glucose samples prior to laboratory analysis [25].

2.5.8 Uptake of, and Adherence to, Preventive Interventions

On the basis of obesity studies and expert advice we assume that 60% of individuals identified with IGR are referred to and start a lifestyle intervention program.

Evidence statement 18 in Review 3 relates to adherence in translational studies and is based on 2 studies. It reports a mean adherence of 10 out of 14 weeks' attendance (i.e. 70%) in one and 40% managing 40 weeks on weigh-in in another study. We have therefore assumed an average level of adherence of 55%. For the purposes of costing interventions, we assume that costs cannot be reduced as a result of non-adherence because all individuals begin the program and participation may be intermittent. For subsequent years, it is assumed that there is scalability on the basis that many of those with poor adherence to the initial core intervention are likely to not participate in maintenance programs.

This assumes that classes run efficiently with an average size of 10-15 but to achieve this may require inviting more (so some classes may be larger and some smaller).

2.5.8.1 Annual Monitoring

For individuals with IGR that do not uptake or persist with preventive interventions, we assume that they are still monitored annually, incurring the cost of an HbA1c test and a nurse appointment.

2.5.9 Pharmacological treatment

Although the effectiveness of metformin in a prevention setting is known from RCTs such as the US DPP, importantly, its effectiveness in those that do not succeed with prior lifestyle interventions is not known. However, the potential impact and cost-effectiveness of this strategy has been evaluated for the HTA monograph on prevention strategies (in press) and found to be cost-effective and have drug-based strategies from detection of IGR (Gillies et al).

Orlistat is also potentially an option for some individuals as it is known to be a cost-effective intervention for weight loss. We have not modelled the cost-effectiveness of orlistat as it can only be used for two years and does not have a direct effect on glucose tolerance (only an indirect effect due to weight loss) and would seem an inferior option compared to metformin if the primary aim is reducing risk of progression to diabetes. All interventions (including drugs and surgery) which are already of demonstrated cost-effectiveness in obesity will be of equal or greater cost-effectiveness in a population with additional risk factors for diabetes.

2.5.10   Effect of risk assessment on medication use

The DPP 2005 reported a 28% lower use of antihypertensive therapy and 25% lower lipid-lowering therapy in the intervention arm [51]. However, in the context of the established CVD risk assessment within NHS Health Checks, use of such medication may already be largely optimised and in real-world setting, the size of any reduction in medication use would likely be smaller. Therefore, we conservatively assume no benefit from risk assessment in terms of reduced use of such drugs.

2.5.11   Role of risk stratification in targeting those at highest risk of diabetes

Financial and resource constraints in the NHS means that it may not be possible to offer an intensive intervention to all individuals with IGR. In such circumstances, targeting intensive interventions towards those at highest risk of diabetes makes clinical and economic sense. Within the NHS, people are often stratified for access to obesity interventions so this would not be a new practice.

2.5.11.1   Predicting Risk of progression from Impaired Glucose Regulation to Type 2 Diabetes

Such targeting of intensive interventions can be aided by use of scores and algorithms to estimate a person's risk of future progression from IGR to diabetes. Such risk stratification also desirable because not all patients progress even in the absence of intervention.

There is an argument that, although glucose is clearly of prognostic significance, risk stratification should not be based solely on an arbitrary glucose-based cut-point. The alternative is use of a risk score, the Finnish FINDRISC score having been shown to be a good indicator of an individual's propensity to progress given their risk factors, even though it does not include any glucose measurement (other than any history of a previous abnormal glucose test)[36]. The baseline FINDRISC score is also a strong predictor of the effectiveness of intervention [52].

Bonora [53] showed that HbA1c was highly predictive of progression, even after adjustment for age and sex, LDL and HDL cholesterol levels, log-transformed triglyceride levels, BMI, waist-to-hip ratio, hypertension, family history of diabetes, education, alcohol use, physical activity score, and smoking status. This confirms that joint assessment of risk based on glucose and FINDRISC parameters is required to stratify individuals optimally. Decisions around prioritising treatments of varying intensity could then be made on the basis of both glucose levels and other risk factors. To some extent, this would be occurring implicitly as a consequence of combined use of a risk score and glucose levels for the initial identification of IGR.

Unfortunately, no published evidence of such a score or algorithm to enable the joint assessment of risk has yet been identified, although it is likely that datasets exist from which this could be derived.

Selvin [54] suggested a dual role for HbA1c and fasting glucose as both strongly predict subsequent risk of diagnosed diabetes with the very high risk observed for persons with both elevated fasting glucose and HbA1c . Whether both have predictive value in a multivariate analysis alongside FINDRISC variables warrants further research.

Note of caution

In the Finnish DPS treating the highest risk was clearly most effective in terms of the absolute risk reduction and therefore most cost-effective [52]. However, it seems that little is known about the relative reduction in risk of diabetes from intervening in individuals at varying baseline points along the continuum of glucose levels from onset of IGR through to onset of diabetes. More evidence on this is needed and could alter assumed priority groups for intervention.

2.5.11.2 **Modifiable risk**

Although more complex, the concept of modifiable risk is worth considering, the aim being to treat those that are likely to benefit most from intervention. This would entail a calculation of how much the risk would be reduced given the typical weight (or physical activity) change that could be expected. This could be done using change in weight (or BMI or waist circumference), or alternatively potential change in glucose, or ideally (evidence permitting) both of these. A simple approach is to calculate the person's risk using a risk score algorithm and then calculate the reduction in risk based on the typical expected change in weight:

$$\text{Expected reduction in risk} = \text{absolute risk of diabetes over 10 Years} \times (1 - (1-0.16)^k)$$

where 0.16 is the relative risk reduction per kg of weight loss (Hamman [37]), and k = potential sustained weight loss measured in kg

2.6   **Structure of Economic Model**

2.6.1 Risk assessment module

The risk assessment module is a simple analysis of the LEADER dataset mapping each individual to their risk assessment outcome according to whether they take up (and complete) risk assessment, their risk score and glucose level. Depending on whether a person has a true or false outcome from risk assessment, each individual is then mapped to an initial treatment pathway as set out in

2.6.2 Risk assessment Outcomes of Interest

As well as the cost-per-case detected, other considerations which will influence commissioners are –

4) What will it cost commissioners in up-front investment to implement interventions?
5) How many blood tests would this involve?
6) How does increasing the amount of investment and choice of risk assessment strategy affect the number of cases of diabetes that can be delayed/prevented?

Table 7 earlier. The cost-per-case detected is calculated from aggregating the costs of risk assessment according to the need for and uptake of each stage, and dividing by the number of cases of IGR and diabetes detected.

2.6.3 Prevention of diabetes module

The prevention module models the year-on-year glycaemic status of individuals identified with IGR through risk assessment. This entails a model of the risk of, and natural history of, progression from IGR to diabetes, overlaid with the effect of preventive intervention to reduce the risk of diabetes, which is either in the form of a direct relative risk for the benefit of intervention compared to no intervention, or a marker for the reduction in risk which is taken to be weight loss.

2.6.4 Treatment of diabetes model

2.6.4.1 Summary of the Sheffield Diabetes Model

The Sheffield Diabetes Model is a holistic health state simulation model of the natural history of diabetes and the lifetime cost effectiveness of different treatments for type 2 diabetes. The model replicates patients' risk of progression through five co-morbidities: retinopathy, nephropathy, neuropathy, coronary heart disease (CHD), and cerebrovascular disease. The original model is largely based on the Eastman model [55] [56] in which patients using results from the Diabetes Control and Complications Trial (DCCT). Patients can experience three of the major complications associated with diabetes, neuropathy, nephropathy and retinopathy. The time spent by patients in each state for each co-morbidity is recorded, e.g. years spent on dialysis, severe vision loss etc., together with transitions between states. Total costs are obtained by adding the costs of therapy, the costs of one-off treatments (e.g. cost of amputation), and on-going treatment of complications (e.g. treatment following stroke). The health benefit, the incremental quality-adjusted life-years, is obtained by applying quality of life measures (such as preference scores from the Harvard web-based database) to the time spent in the various diabetic health states. Cost effectiveness estimates for potential interventions are obtained by dividing the total costs by the incremental QALYs.

2.6.4.2 Detailed Description

More details of the Sheffield Type 2 Diabetes Model are provided in Appendix 6 . It is important to highlight key parameter values and assumptions that are significant for this evaluation and these are covered in Section 2.6.5 below.

2.6.5 Key model components, parameter values and assumptions for this evaluation

2.6.5.1 Long-term Risk of Complications of IGR and diabetes

The greatest burden of disease arising from diabetes is the increased risk of CVD relative to people without diabetes or IGR. Risk of CVD is estimated modelled via the UKPDS risk engines for coronary heart disease (CHD) and stroke (UKPDS56 [57] and UKPDS60 [58] respectively). The CHD equation includes HbA1c so has a parameter that captures the continuum of risk as HbA1c increases from the NGT range through to diabetes (although 2 hour glucose might correlate more closely with CHD risk in the range from NGT to early or pre-clinical diabetes).

Similarly, HbA1c is a risk factor for microvascular complications such as retinopathy, nephropathy, and neuropathy.

2.6.5.2 Antihyperglycaemic medication

Another benefit from interventions to prevent diabetes is the reduction in need and cost of medication to control blood glucose levels. In particular, antihyperglycaemic medication is currently generally expensive once a patient reaches the point of 2nd-line treatment failure with oral hypoglycaemic agents (OHAs).

Table 11 : Dosing and Price of OHAs and Insulin

Therapy	Dose	Unit Cost (BNF 61 [59])	Cost per day
Metformin	x3 per day	£ 1.57 per 56 pack of 500mg £ 1.67 per 84 pack 850mg	£ 0.07 Based on average per of 500mg & 850mg tablets
Sulphonylurea (gliclazide)	Average 210mg/day assumed [60]	60-tab 80mg pack = £1.52	£ 0.07
Sulphonylurea (gliclazide MR)	Assumed equivalent of 210mg gliclazide (30mg of MR formulation $\cong$ 80mg of non-MR formulation per BNF61 [59])	60-tab 30mg pack = £4.38	£0.19
Sulphonylurea (average UK cost)	Based on use of non-MR and MR formulations of gliclazide in ratio 8:1	-	£ 0.08
Insulin	Dose is variable according	The use of insulin glargine (Lantus) has	Varies according

to year since initiation of insulin	increased considerably recently, as to a lesser extent has insulin detemir. The cost of glargine is considered to be a reasonable estimate of the average cost of insulins currently used for Type 2 diabetes in the UK £26 per 1000 i.u.	to dose; 60 units per day = £ 1.96 per day incl. needles/consumables /education

We are assuming that 2nd line OHA therapy for the majority of patients is the addition to metformin of a sulphonylurea in line with NICE recommendations, although there is evidence for increasing use of newer more expensive therapy such as DPP IV inhibitors which have fewer side effects. For the economic model, treatment after 2nd-line failure with OHAs is assumed to be insulin therapy plus metformin.

2.6.5.3 Annual cost of monitoring for patients with diabetes

At £ 177 per patient, the annual cost of monitoring for individuals with diabetes is significant and is broken down below.

Table 12 : Cost of monitoring patients with Type 2 diabetes

Resource	Assumed combined visits for blood pressure & glucose monitoring	Unit Cost (Curtis 2010 [45])	Inflation Uplift Factor	Cost
Nurse at GP (to check HbA1c & proteinuria, pulse check, feet, flu jab)	2	£12.00	1.04	£25
GP clinic	2	£36	1.04	£75
Dietitian	0.5	£34	1.04	£18
HbA1c test	2	£14.00	1.00	£28
Eye screening (now assumed annual)		£21.00	1.50	£31
Total cost				£177

Inflation Uplift Factors, apart from the latest year, are calculated from inflation indices in Curtis 2010 [45]

2.6.5.4 Relationship between Weight Loss and change in Health-related Quality-of-Life (HRQoL)

Based on a simple weighted average of the 4 studies shown in Table 13 below, the model applies a 0.0025 increase in HRQoL per kg of weight loss. A recent review of weight and QoL reported similar results [61].

Table 13 : Utility gain per kg weight loss from weight-loss studies

Trial	Intervention	Patients	Utility gain per kg lost
SAT [62]	sibutramine	362 in total	0.00297
SAT [62]	placebo		0.00472
HTA sibutramine assessment for NICE [63]	sibutramine	308	0.00185

			95% CI = 0.00048-0.00322
	placebo		0.00142
HTA sibutramine assessment for NICE [63]		216	95% CI = 0.00058-0.00341

2.6.6 Other assumptions and perspective

An individuals' use or otherwise of statin use is determined in accordance with their calculated 10-year CVD risk and NICE guidance [64].

Estimates of the incidence per annum of severe hypoglycaemic attacks (hypos) are 1.5% for sulphonylureas and 15% for insulin (ScHARR unpublished review).

The evaluation is carried out from a public sector perspective. For example, costs of preventive interventions potentially delivered by local authorities' health and fitness trainers are included.

Indirect costs to the individual such as the cost of time off work arising from diabetes-related co-morbidities, and time to travel to lifestyle education classes, are not included.

2.7   South Asians of 25-39 years of age – differential evidence used

The LEADER dataset has a data field which indicates if a person is of South Asian ethnicity. A subset specific to South Asians of 25-39 years of age was therefore available to determine risk assessment outcomes for this group .

The other key evidence for South Asians used for the economic modelling, especially where is differs from that for the overall 40-74 population, is summarised in Table 14 below.

Table 14 : Evidence applicable to South Asians

Issue	Evidence	Assumption adopted (where applicable)
Prevalence of IGR and diabetes	Black and Minority Ethnic (BME) groups are at particularly high risk of abnormal glucose tolerance and T2DM, with reported prevalence 2–6 times that of the background white European population [65].	The higher prevalence is reflected in the LEADER dataset (OGTT-defined prevalence 17.3% for IGR, and 4.5% for diabetes [65]) on which the analysis of risk assessment outcomes was based.
Natural history of IGR	There are some data on the effect of ethnicity on progression from IGR to diabetes. In the DPP [21 (table 2)] the data suggest that baseline conversion rates were similar (with a weak trend for about 20% higher conversion in non-whites) although it is unclear if the Asian were of East or South origin. In the DREAM prevention study, South Asians had a Hazard Ratio (HR) of 2.2 versus Europeans [66]. Other studies have shown an Odds Ratio of 2.9 [67], giving a HR = 2.9/((1- 4.1%)+(4.1%*2.9)) = 2.7	Applied a Hazard Ratio of 2.5 for progression from IGR to diabetes for South Asians (SA) versus whites.) . Given the proportion of South Asians in the LEADER study is28%, the Hazard Ratio for SA versus LEADER overall population = 2.5/((2.5*28%)+(1*72%)) = 1.76
Intervention Cost	Course takes twice as long to deliver courses if participants do not speak English. However, If given only the option of a class in English, South Asians would attend that. In addition, if they were told that class in SA language takes twice as long, then they might opt for the English version so it is uncertain as to whether intervention for South Asians would actually cost more	Provide results for two alternative scenarios – one with the same cost as for the overall group, and one with 50% higher cost on average for South Asians (note some specific ethnicities have a high proportion speaking English so not all would need a course in SA)
Effectiveness of preventive Interventions	Evidence from the DPP [68] suggests that lifestyle interventions are less effective in younger age groups in general. However, the DPP also suggests that there could be greater benefit in non-whites than whites, both with Lifestyle Intervention and metformin [21] (although this is relatively weak data).	Given this uncertainty and advice from the PDG, we assumed effectiveness is the same in for South Asians of age 25-39 as for whites of age 40-74 years.
Risk of complications	CHD : in the UK mortality from CHD is currently 46% higher for men and 51% for women in south Asians compared to the general population (assume same for NF events) [69]	Taking the average for men and women, applied a multiplier of 1.485 to the risk of a CHD event
Risk of renal		Same rate as for overall population

disease		
Uptake of risk scores and glucose tests		Same rate as for overall population
Uptake of, and adherence to, preventive interventions		Same rate as for overall population

3. ECONOMIC MODELLING – RESULTS

3.1   Cost per Case Detected

The outcomes and cost-per-case detected for the risk assessment strategies shown previously (Table 4) are shown in Table 15 below. Numbers of blood tests and individuals labelled as having IGR or diabetes are shown per 100,000 population. The size of the population in the 40-74 age group is 19,169,713. The England population in the wider 30-74 age group is 25,709,089.

The variation in prevalence figures according to the different tests and cut-points demonstrates the problem of comparing strategies using arbitrary definitions of IGR and diabetes.

Table 15 : Outcomes and cost-per-case detected for alternative risk assessment strategies

Risk assessment Strategy	Risk score & cut-point	Glucose test and cut-point for IGR	Prevalence of undiagnosed IGR / diabetes (see note)	Blood tests (per 100,000 eligible population)	Cost of risk assessment (per 100,000 eligible population)	Cases of IGR/Diabetes detected (per 100,000 eligible population)	Cost Per Eligible Person for risk assessment	Cost-per-case of IGR/Diabetes detected
				Adjusted for uptake of each stage of risk assessment				
0	Vascular Checks Algorithm : BMI≥30 (or 27.5 for South Asians) or HxHT or BP ≥140/90	FPG ≥ 6 mmol/L	3.2% / 6.4%	-	-	-	-	-
1	LSA ≥ 10 points	HbA1c ≥ 5.7%	44.3% / 5.8%	32,896	724,640	15158 / 1962	£7.25	£42
2	LSA ≥ 13 points	HbA1c ≥ 5.7%		28,188	658,728	13178 / 1862	£6.59	£44
3	LSA ≥ 16 points	HbA1c ≥ 5.7%		22,408	577,808	10762 / 1691	£5.78	£46
4	LSA ≥ 10 points	HbA1c ≥ 5.85%	25.5% / 5.8%	32,896	724,640	9128 / 1962	£7.25	£65
5	LSA ≥ 13 points	HbA1c ≥ 5.85%		28,188	658,728	8076 / 1862	£6.59	£66
6	LSA ≥ 16 points	HbA1c ≥ 5.85%		22,408	577,808	6847 / 1691	£5.78	£68
7	LSA ≥ 10 points	HbA1c ≥ 6.0%	18.0% / 5.8%	32,896	724,640	6570 / 1962	£7.25	£85
8	LSA ≥ 13 points	HbA1c ≥ 6.0%		28,188	658,728	5886 / 1862	£6.59	£85
9	LSA ≥ 16 points	HbA1c ≥ 6.0%		22,408	577,808	5043 / 1691	£5.78	£86
10	LPDS ≥ 4.75	HbA1c ≥ 5.7%	44.3% / 5.8%	64,486	925,604	29793 / 3742	£9.26	£28
11	LPDS ≥ 5.0	HbA1c ≥ 5.7%		56,529	814,203	26844 / 3574	£8.14	£27
12	LPDS ≥ 5.25	HbA1c ≥ 5.7%		47,280	684,714	23000 / 3380	£6.85	£26
13	LPDS ≥ 4.75	HbA1c ≥ 5.85%	25.5% / 5.8%	64,486	925,604	17755 / 3742	£9.26	£43
14	LPDS ≥ 5.0	HbA1c ≥ 5.85%		56,529	814,203	16265 / 3574	£8.14	£41
15	LPDS ≥ 5.25	HbA1c ≥ 5.85%		47,280	684,714	14395 / 3380	£6.85	£39

16	LPDS ≥ 4.75	HbA1c ≥ 6.0%		64,486	925,604	12717 / 3742	£9.26	£56
17	LPDS ≥ 5.0	HbA1c ≥ 6.0%	18.0% / 5.8%	56,529	814,203	11774 / 3574	£8.14	£53
18	LPDS ≥ 5.25	HbA1c ≥ 6.0%		47,280	684,714	10573 / 3380	£6.85	£49
19	LPDS ≥ 4.75	FPG ≥ 5.5		55,056	897,260	13830 / 1042	£8.97	£60
20	LPDS ≥ 5.0	FPG ≥ 5.5	23.5% / 1.8%	48,173	576,804	12549 / 999	£5.77	£43
21	LPDS ≥ 5.25	FPG ≥ 5.5		40,077	483,700	11127 / 883	£4.84	£40
22	LPDS ≥ 4.75	FPG ≥ 5.7		55,056	655,963	9248 / 1042	£6.56	£64
23	LPDS ≥ 5.0	FPG ≥ 5.7	15.4% / 1.8%	48,173	576,804	8551 / 999	£5.77	£60
24	LPDS ≥ 5.25	FPG ≥ 5.7		40,077	483,700	7660 / 883	£4.84	£57
25	LPDS ≥ 4.75	FPG ≥ 6.0		55,056	655,963	5066 / 1042	£6.56	£107
26	LPDS ≥ 5.0	FPG ≥ 6.0	8.2% / 1.8%	48,173	576,804	4771 / 999	£5.77	£100
27	LPDS ≥ 5.25	FPG ≥ 6.0		40,077	483,700	4368 / 883	£4.84	£92

BP = blood pressure; HxHt = treated hypertension

Note :
In the fourth column of each row, e.g. 3.2% /6.4%, the first number shows the percentage of the population expected to have a high probability of progression to type 2 diabetes based on the LEADER study, while the second number shows the percentage expected to have undiagnosed type 2 diabetes.
The second percentage is based on established criteria for undiagnosed diabetes for the relevant test (i.e. ≥ 6.5% for HbA1c; >=7.0 mmol/L for FPG; WHO criteria for OGTT).
The first percentage is based on more arbitrary glucose-based definitions of what constitutes an individual having a high probability of progression to diabetes. For rows S1 to S3, the percentage is 44.3%, which is the proportion of the population with an HbA1c level between 5.7% and 6.4% inclusive. That is, the HbA1c cut-off level defines the percentage or proportion with a high probability of progression. In the same way, for rows S4 to S6, as the lower HbA1c cut-off is raised to from 5.7% to 5.85%, the proportion that are regarded at high risk of progression to diabetes falls to 25.5%, and the same logic is applied for the rows S7 to S18. Because of the varying criteria used to define 'high risk' or IGR, care is required in the interpretation of the 'cost per IGR and diabetes detected' figures in the last column of the table. As these figures reflect the cost of identifying individuals according to varying criteria for IGR, they cannot be used as a shortcut to determining an optimal strategy in terms of cost-per-case detected. The figures do however form part of the calculation of the overall long-term cost-effectiveness of alternative strategies.

Strategies involving LSA with an FPG test are not shown because it became clear from analysis of LSA with HbA1c tests that LPDS was a superior option

3.1.1.1 Narrowing down options: HbA1c- based testing

We applied the following criteria to selecting which strategies on which to undertake full economic evaluation :

- detects at least 80% of cases of undiagnosed diabetes (defined by HbA1c or FPG as appropriate)
- eliminates, at the risk score stage, at least 20% of individuals
- LSA is more expensive than LPDS so can be excluded as a preferred option (although may be appropriate for individuals lacking the requisite data in GP records to calculate the LPDS)

To illustrate the kind of trade-offs between alternative risk assessment strategies, from Table 15 above, it can be seen that :

- S10 identifies a large number with IGR with a low cost per case detected
- S18 identifies fewer with IGR (but higher risk) and higher cost per case
- S14 is compromise between the two above

3.1.1.2 Narrowing down options : FPG- based testing

A relatively low FPG cut-point of 5.5 mmol/L (i.e. much lower than the 6.0 mmol/L threshold often used to define IGR) was considered necessary in order to identify a sufficiently high proportion of individuals as being at high risk of diabetes so that they would receive an intervention.

This low cut-point may be in part a reflection of the fact that plasma glucose samples outside of a research environment are often kept at 4 - 8°C for up to 2 hours which could lead to reduced glucose levels, this being suggested for the LEADER dataset [25].

3.2   Long-term modelling results

3.2.1 Cost effectiveness results – reporting conventions

To compare the cost effectiveness of alternatives risk assessment strategies, the steps are –

i) calculate the difference in total lifetime costs arising (including risk assessment and treatments) – this is the incremental costs

ii) calculate the difference in total lifetime QALYs arising (including risk assessment and treatments) – this is the incremental QALYS

The ratio between the incremental costs and QALYs gives the incremental cost per QALY or incremental cost-effectiveness ratio (ICER). This can be compared with the threshold by which interventions are judged to be cost-effective, which is in the range £ 20,000 - £ 30,000 per QALY. This ratio can be confusing to interpret however, if either incremental costs or incremental QALYs are negative, which is the case for this

analysis. We have therefore presented an alternative measure, net benefit, instead. A positive net benefit (treatment B minus A) indicates that strategy B is cost-effective, and vice versa.

If an intervention results in both cost savings and health gains (QALYs), then it is said to dominate the comparator.

3.2.2 Interim results

Appendix 7, the outcome risk assessment on subsequent pathways were being determined according to an arbitrary strategy-specific glucose cut-point, e.g. HbA1c >=6%, to separate cases of normal glucose tolerance and IGR.

For the interim results presented in the tables in

It became clear that it would not be possible to make a fair comparison of the cost-effectiveness between alternative risk assessment strategies, even for alternative cut-points of the same glucose test, e.g. HbA1c, the reason being that the alternative cut-offs for IGR/NGT lead to arbitrary differences in the proportions labelled as IGR versus NGT, and hence the prognosis of individuals in the model.

It was however possible to compare, *for the same risk assessment of alternative intensities of intervention to prevent diabetes in the tables in*

Appendix 7 show that more intensive interventions are more cost-effective than less intensive ones.

3.2.3 Final results – overall cohort

The methodology for calculating an individual's risk of progression from IGR to diabetes was subsequently amended so that it took account of their HbA1c level at risk assessment, rather than an arbitrary classification as NGT or IGR using strategy-specific HbA1c cut-points . The cost-effectiveness of alternative tests and cut-points can now be compared directly.

The results are shown in Table 16 and Table 17 below, the latter assuming the those identified at high risk of diabetes with the Vascular Checks program are actually eligible for an intervention to prevent diabetes.

The interim results (per Section 3.2.2 above) suggested that intensive intervention was more cost-effective than less intensive ones. Therefore, for the final results in this section, where strategies involve an intervention, only the most intensive intervention scenarios were adopted, i.e. costing £ 150 in the first year (per Table 9 earlier) and maintenance sessions every 4 months for years 2 to 4 (per

Table 10 earlier).

Table 16 : Cost-Effectiveness of Risk assessment versus Vascular Checks (without intervention)

Risk assessment algorithm	Total Costs	Total QALYs	Incr. Costs vs Vascular Checks (no intvn)	Incr. QALYs vs Vascular Checks (no intvn)	CE Ratio (per QALY), Cost-effective versus Vascular Checks?
	Per person eligible for risk assessment				
Vascular Checks Algorithm (no intervention)	£ 10,650	10.8387	-	-	-
LPDS ≥ 4.75, HbA1c ≥ 5.7% (+ intensive intervention)	£11,121	10.8779	£ 472	0.0392	£ 12,042 Yes
LPDS ≥ 5.0, HbA1c ≥ 5.85% (+ intensive intervention)	£10,884	10.8597	£ 234	0.0210	£ 11,169 Yes
LPDS ≥ 5.25, HbA1c ≥ 6.0% (+ intensive intervention)	£10,780	10.8502	£ 131	0.0115	£ 11,376 Yes
LPDS ≥ 5.25, FPG ≥ 5.5mmol/L (+ intensive intervention)	£ 10,740	10.8515	£90	0.0128	£ 7,057 Yes

Table 17 : Cost-Effectiveness of Risk assessment versus Vascular Checks (with intervention)

Risk assessment algorithm	Total Costs	Total QALYs	Incr. Costs vs Vascular Checks (+ intvn)	Incr. QALYs vs Vascular Checks (+ intvn)	CE Ratio (per QALY), Cost-effective versus Vascular Checks ?
	Per person eligible for risk assessment				
Vascular Checks Algorithm (with intensive intervention)	£10,589	10.8403	-	-	-
LPDS ≥ 4.75, HbA1c ≥ 5.7% (+ intensive intervention)	£11,121	10.8779	£533	0.0376	£ 14,154 Yes
LPDS ≥ 5.0, HbA1c ≥ 5.85% (+ intensive intervention)	£10,884	10.8597	£295	0.0194	£ 15,192 Yes
LPDS ≥ 5.25, HbA1c ≥ 6.0% (+ intensive intervention)	£10,780	10.8502	£192	0.0100	£ 19,259 Yes
LPDS ≥ 5.25, FPG ≥ 5.5mmol/L (+ intensive intervention)	£ 10,740	10.8515	£151	0.0113	£ 13,440 Yes

3.2.3.1 Incremental analysis : HbA1c-based testing (overall 40-74 age group)

This analysis, for the 40-74 age group, shows the incremental costs and QALYs and cost per QALY of progressively lowering the risk score cut-point for HbA1c testing and the criteria for assigning individuals as having IGR (and receiving intensive intervention)

Table 18 : incremental costs and QALYs and cost per QALY of lowering the cut-points

Risk assessment algorithm	Total Costs	Total QALYs	Incremental Costs	Incremental QALYs	Cost per QALY
	Per person eligible for risk assessment				
Vascular Checks Algorithm (without intvn)	£10,650	10.8387	-	-	-
LPDS ≥ 5.25, HbA1c ≥ 6.0% (with intensive intvn)	£10,780	10.8502	£130	0.0115	£11,304
LPDS ≥ 5.0, HbA1c ≥ 5.85% (with intensive intvn)	£10,884	10.8597	£104	0.0095	£10,947
LPDS ≥ 4.75, HbA1c ≥ 5.7% (with intensive intvn)	£11,121	10.8779	£237	0.0182	£13,022

Figures are per person eligible for risk assessment

This suggests that intervening in individuals that meet the risk score criteria and with an HbA1c between 5.7% and 6.0%, is likely to be cost-effective.

3.2.4 Final results – South Asians of 25-39 years of age

Table 19 : Cost-Effectiveness of Risk assessment versus Vascular Checks (without intervention)

Risk assessment algorithm	Total Costs	Total QALYs	Incr. Costs vs Vascular Checks (no intvn)	Incr. QALYs vs Vascular Checks (no intvn)	CE Ratio (per QALY), Cost-effective versus Vascular Checks ?
	Per person eligible for risk assessment				
Vascular Checks Algorithm (no intvn)	£14,955	15.4924	-	-	-
LPDS ≥ 5.25, HbA1c ≥ 6.0%	£ 14,675	15.5211	- £ 280	0.0287	Cost-effective (intervention dominates – see note)

Note - intervention A is said to dominate intervention B if it yields both cost savings and health gains (i.e. more QALYs) compared to B

<u>Sensitivity Analysis</u>

Assuming a 50% higher intervention cost (to take account of longer course delivery times for non-English speaking participants) makes little difference to the results.

3.2.4.1 Cost Savings and QALY gains for South Asians of age 25-39 – a breakdown

Costs :

The model predicts that risk assessment in a group of South Asians age 25-39 will be cost saving in the long run (compared to no intervention).

The cost saving is mainly due to large reductions in the incidence of dialysis and associated costs, whereas the reduction in dialysis was only small in the overall 40-74 group. These findings are explained by the baseline (without intervention) incidence of dialysis being 7.5 times higher in the 25-39 South Asian group than the 40-74 group. As a result, intervention yields a much greater absolute reduction in the incidence of dialysis in the 25-39 South Asian group.

To explain the higher baseline incidence of dialysis in this younger South Asian group, firstly, they are at higher risk of progression from IGR to diabetes (Hazard Ratio 1.76) and therefore greater likelihood of developing renal disease. Equally, the 40-74 group are on average 24 years older at risk assessment than the 25-39 group (57 years versus 33 years respectively). The average age at diagnosis of diabetes will be greater than these ages. Many years are typically required for renal disease to develop and progress from microalbuminuria to end-stage renal disease. In the 40-74 group, the incidence of dialysis is much negated by the competing risks of CVD (and other-cause mortality) which are strongly influenced by age. However, those in the 25-39 group that have or develop diabetes are more likely to have a sufficiently prolonged exposure to microvascular damage to allow them to reach end-stage renal disease and therefore receive dialysis.

The lifetime incidence of dialysis, time spent in dialysis and average cost from simulations of 64,552 individuals are shown in Table 20 below (using LPDS cut-point ≥ 5.25 points and Hba1c ≥ 6.0% to define IGR).

Table 20 : The lifetime incidence of dialysis, time spent in dialysis and average cost per person

| | South Asians age 25-39 | | Overall 40-74 group of mixed ethnicity | |
| | N = 64,552 | | N = 64,552 | |
	Risk assessment & intervention	Vasc checks with no intvn	Risk assessment & intervention	Vasc checks with no intvn
Incidence of dialysis	8,438	9,745	1,037	1,301
Total Years in dialysis state	29,891	34,062	3,408	4,273
Years spent in dialysis state (on average for those starting dialysis)	3.5	3.5	3.3	3.3
Cost of dialysis averaged across all 64,552 individuals eligible for risk assessment	£4,138	£4,725	£547	£695

QALYs :

The QALY difference is mainly due to greater Life Years Gained resulting from fewer CVD and renal-related deaths, even though this is offset through subsequent greater other-cause (non-vascular) mortality.

Table 21 : Causes of mortality

	South Asians age 25-39 N = 64,552		Overall 40-74 group N = 64,552	
	Risk assessment & intervention	Vasc checks with no intvn	Risk assessment & intervention	Vasc checks with no intvn
CVD deaths	36,409	36,502	22,462	22,609
Renal deaths	2,427	2,791	257	337
Deaths from other causes	25,716	25,259	41,833	41,606

Sensitivity Analysis :

A limitation of the above estimates is the source of epidemiological data underpinning the risks of renal disease. As renal disease results from ongoing microvascular damage, duration of diabetes is clearly an important determinant of the incidence of renal disease and the risks are appropriately stated as a function of duration of diabetes. However, the risks originate from studies of individuals with type 2 diabetes having a more typical age at diagnosis. If the risks in a younger cohort are actually lower, there may be some overestimation of benefits from risk assessment and intervention in the 25-39 South Asian group. Conversely, South Asians have been shown to be at higher risk of renal disease than whites in one study [70], and the time spent once on dialysis may be underestimated as young patients with end-stage renal disease live longer [71]).

As a sensitivity analysis, assuming that the actual dialysis cost savings and renal-related survival benefit are 50% lower in this younger cohort, risk assessment and intervention would yield incremental costs of £ 13 and incremental QALYs of 0.0172 and an ICER of £ 768, i.e. it would still be highly cost effective.

Timing of cost savings

It should be noted that the above cost savings take many years to accrue because of the length of time to progress from early renal disease through to end-stage renal disease and dialysis, as shown by Figure 6 below (cumulative incremental costs comparing i) risk assessment followed by intensive intervention [†] with ii) Vascular Checks without any intervention)

3.2.4.2 South Asians age 25-39 – Marginal Analysis

The analysis undertaken above showed that risk assessment and intervention in this group is likely to be cost-saving. Given that the cost savings are very much downstream, this raises two points –

- what is the optimal age within the 25-39 age band at which to screen this group, is there an age at which risk assessment should start (e.g. 30, 35) ? Unfortunately, this is a more complex marginal analysis beyond the structure of the current economic model.
- although cost saving in the long run, cost savings should not be expected in the short-term - it will take many years for these to accrue

---

[†] Pre-screen LPDS ≥ 5.25 points; Hba1c ≥ 6.0 mmol/l indicating IGR

Figure 6 : Time profile of cost savings and QALY benefits in the 25 -39 South Asian group (average per individual eligible for risk assessment) [‡]
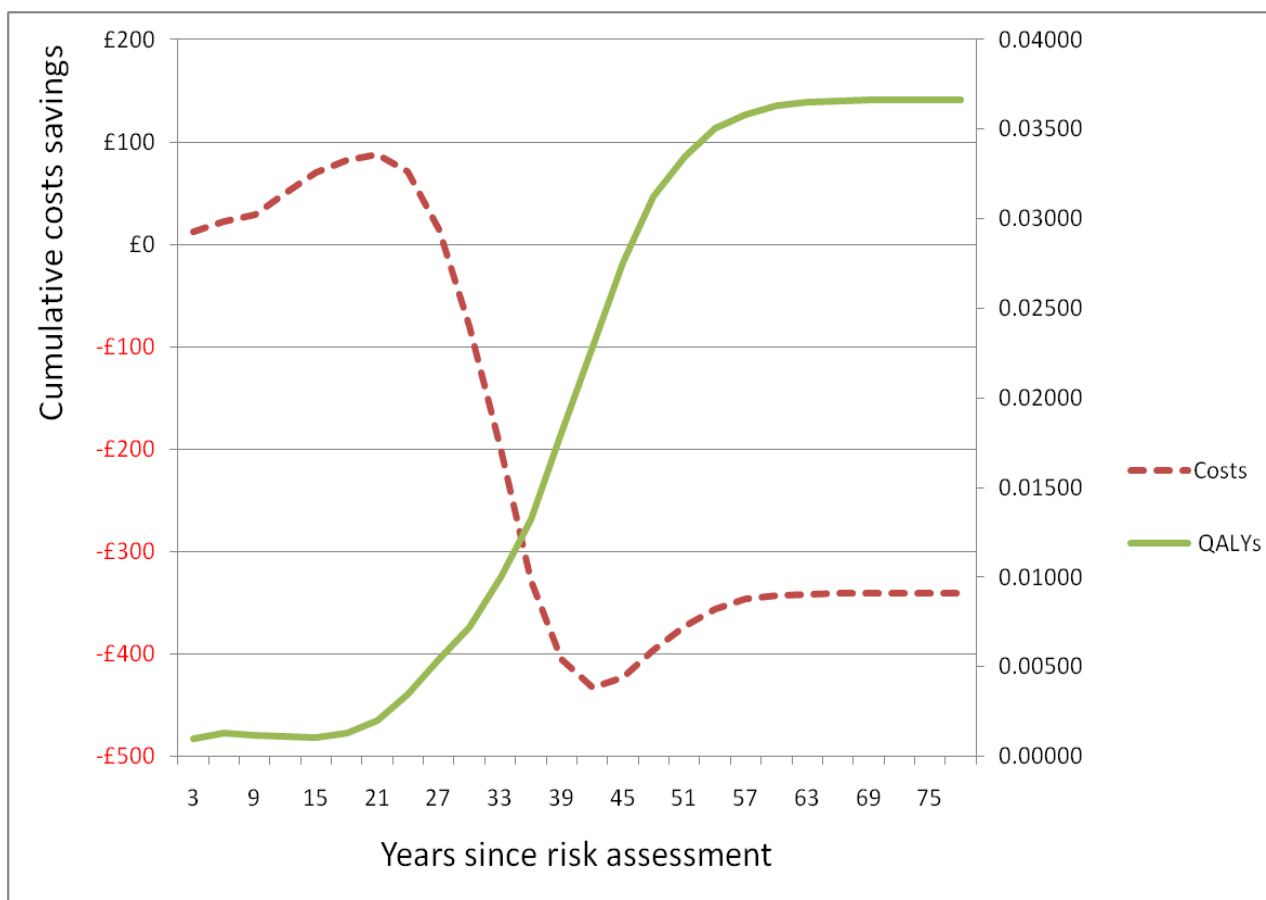
3.2.5 Budget Impact, Payback period and Resource Use

For the broad 40-74 age group, even though risk assessment and intervention appears to be cost effective in the long run, an important additional outcome is how affordable the intervention is initially. Whilst the costs of risk assessment and lifestyle intervention fall largely in the first and subsequent 3 years, cost savings through reduction in complications, reduced costs of monitoring diabetes, and lower diabetes-related therapy costs (especially insulin) accrue over the long-term.

The size of the England population in the 40-74 age band is estimated to be 19,169,713. Per 100,000 individuals within this eligible group, between 60, 000 and 70,000 blood tests would be needed even for a test strategy that does not involve an OGTT, assuming a risk score with close to 100% uptake (e.g. a practice database risk score). Costs of risk assessment based around HbA1c testing are in the region of £ 700,000 to £ 1,000,000 depending on the specific strategy as shown below.

[‡] Note – these figures were from an additional simulation so there are some differences between the lifetime cost and QALY figures but the shape of the curves is the same

4. <u>CONCLUSIONS AND DISCUSSION</u>

4.1   <u>What the results show</u>

The following conclusions are possible:

- intervening in patients identified with IGR to reduce their risk of developing diabetes, while also identifying undiagnosed diabetes, is very likely to be cost-effective compared to identification of undiagnosed diabetes alone within the current Vascular Checks program
- the use of FPG or HbA1c testing to identify individuals at high risk (or with undiagnosed diabetes) appears to be in the cost-effective range compared to OGTT-based testing (as used with the current Vascular Checks program) for the alternative risk assessment strategies evaluated
- more intensive preventive intervention strategies appear to be more cost-effective than less intensive ones

For risk assessment with a risk score plus HbA1c (or FPG), the alternative cut-points determine how many individuals are labelled as IGR/high risk and the average level of risk of diabetes in the group.

The cost savings from delaying or preventing diabetes are modest in the early years – it could be expected to save about £ 200 in annual monitoring costs plus the cost of first-line antihyperglycaemic medication (mainly metformin, a low cost generic) but the majority of the savings in terms of reduced cardiovascular and microvascular clinical events would be further downstream as the age, duration of diabetes and HbA1c increase.

Risk assessment and intervention in South Asians of 25-39 years of age appears to be not only cost-effective but may also be cost-saving. This is because of the greater lifetime risk of dialysis in younger individuals, the higher risk of progression from IGR to diabetes (Hazard Ratio 1.76) in South Asians and higher risk of CHD (Hazard Ratio 1.49) in South Asians. Assuming a 50% higher intervention cost (to take account of longer course delivery times for non-English speaking participants) makes little difference to the results and would not alter the conclusion.

4.2   <u>Management of 'non-responders'</u>

A minority, though significant, proportion of individuals identified as suitable for intervention to reduce their risk of diabetes is not likely to make adequate progress towards reducing their risk through reduction in weight or increase in physical activity. For such patients, continuing with an intensive lifestyle intervention may not be a good use of resources.

4.2.1 Cost-effectiveness of intervention with metformin therapy

Previous work on prevention of diabetes showed that metformin is a cost-effective alternative option for individuals that do not succeed with lifestyle intervention [4]. This does rely on the assumption that a good

response to metformin can still be obtained when used in non-responders to lifestyle intervention, relative to the response in treatment-naive patients as observed in clinical trials. We are not aware of any evidence around this from trials to date.

4.3   Prioritising intensive interventions

Given NHS manpower and budgetary constraints, it may not be possible for all individuals at high risk of diabetes to receive an intensive intervention. Although we have not modelled potential alternative approaches to prioritising, a pragmatic approach to targeting the highest risk is illustrated here –

- HIGHEST: HbA1c >= 6.0% and a very high risk score

- NEXT HIGHEST: HbA1c >= 6.0% and a high risk score

- NEXT: VERY high risk score alone or HbA1c >=5.8%

The above is an illustration but ideally needs calibration using a dataset from a large study of progression from IGR to diabetes.

A further refinement would take account of how much the risk can be reduced rather than baseline risk levels. The following formula from Section 2.5.11.2 could be used to prioritise interventions, although at present we are not aware of published evidence for a calculation of risk that includes the glucose level :

$$\text{Expected reduction in risk} = \text{absolute risk of diabetes over 10 Years} \times (1 - (1-0.16)^k)$$

4.4   Use of FPG or HbA1c

From an economic perspective, our analysis suggests the difference in costs and benefits of risk assessment with a fasting versus HbA1c test are likely to be small in absolute terms.

Factors affecting the relative cost-effectiveness include the cut-points chosen to define those with IGR/at high risk, both the risk of progression and treatment effectiveness according to different baseline glucose profiles (FPG, HbA1c). Additional modelling work on the cost-effectiveness of risk assessment using FPG versus HbA1c may be enhanced by additional primary/secondary research around some of these issues.

4.5   Comparison with other studies

The economic modelling presented at PDG7 reported that risk assessment and intervention to prevent diabetes is likely to be cost-effective. There was however an expectation amongst some PDG members that the cost-effectiveness ratio (or cost per QALY) would be lower. In this respect, the first point to highlight is that results were presented compared against a baseline of the diabetes testing component of the Vascular Checks programme, both with the latter including and not including a preventive intervention for

those identified as being at high risk of diabetes. For comparison with other economic analyses, results compared to Vascular Checks *without* an intervention are most relevant – these show lower cost-per-QALY ratios (in the range £ 11,169 to £ 12,042 per QALY for HbA1c-based risk assessment, compared to £ 14,154 to £ 19,259 per QALY if the Vascular Checks is assumed to *include* a preventive intervention).

Since the consultation process, an analysis of the cost-effectiveness of lowering the HbA1c cut-point for high-cost intervention to prevent diabetes has recently been published by Zhuo et al [72]. This suggests that lowering the HbA1c cut-point from 6.4% in 0.1% increments down to a cut-point of 5.7% results in successive cost-effective incremental health gains but at progressively higher cost-effectiveness ratios. In this US study, the conventional $50,000/QALY cost-effectiveness threshold was used.

4.5.1 *Key issues that should to be taken into account when comparing the results with other modelling studies are, summarised below*

Intervention costs

The interventions that we have modelled differ from those in most other economic analyses in that they are less intensive and reflect what is realistic in clinical practice rather than possible in clinical trials.

Based on evidence from review 3, the results presented at PDG7 were based around an initial preventive intervention costing £ 150 that could finance a program in the first year involving –

- 11 core sessions

- each session lasting 1 hour 15 minutes, with 45 minutes preparation time (which PDG members commented might be too much)

- 2 educators per group

- course delivery by a (top of) band 5 NHS professional, salary (excluding on-costs) £ 27,625

- Inclusion of a free pedometer (worth £ 10)

There is some debate as to whether the group size could be increased beyond the 8-10 typically adopted in the UK for similar courses. Larger class sizes, in the range 13-17, were adopted in DPP translation studies seemingly without loss of effectiveness.

Non-responders to intervention

At present, we have assumed that all individuals starting a course to prevent progression to diabetes continue into the maintenance phases (subject to adherence) regardless of their response to the initial intervention. We could (but have not to date) however assume that a proportion of individuals do not enter the maintenance intervention phase if they do not achieve a satisfactory weight loss (or increase in physical activity).
Such a revised assumption would be likely to have a significant effect on the cost-effectiveness ratio.

Durability of weight loss

The assumptions adopted on durability of weight loss are based on observations from heterogeneous studies and are therefore uncertain. The results presented at PDG7 for intensive intervention assume that the initial weight loss following intervention is gradually regained such that is has been completely regained 8 years from the start of the initial intervention.

Effectiveness of intervention in individuals identified at high risk of diabetes using an HbA1c

As there is a lack of good evidence for successful intervention in this group of patients, it was agreed with the economics subgroup that it would be assumed that the effectiveness is 75% of that demonstrated in OGTT-identified groups. The rationale for this conservative approach is in part the fact that HbA1c-identified individuals may have a different underlying impairment of glucose regulation, and therefore may have a different response to intervention.

Timing of cost savings

The cost savings from delaying or preventing a case of diabetes are modest in the early years – it could be expected to save about £ 200 in annual monitoring costs + the costs of metformin (plus sulphonylureas for some patients) but the majority of the savings in terms of reduced cardiovascular and microvascular clinical events would be further downstream as the age, duration of diabetes and HbA1c increase.

Effect of metformin on risk of CHD

The modelling inevitably includes the perverse effect that delaying diabetes also delays starting metformin which, to the best of current knowledge, has a considerable effect on reducing CHD risk (which we estimated at 23% independent of glucose reduction) - there are ongoing or planned trials to test out whether metformin would reduce CHD risk in patients at risk of diabetes.

4.6   Conclusions in conjunction with other studies

- Interventions to prevent progression from IGR to diabetes are cost-effective

- Risk assessment for diabetes/IGR followed by preventive intervention is likely to be cost-effective

- For Hba1c-based testing, the choice of Hba1c cut-point for preventive intervention to prevent diabetes clearly has a big impact on the total number of cases of IGR identifiable (and therefore the proportion of cases of diabetes that are preventable), but the impact on cost-effectiveness is less certain. Similar to our findings, recent work by Zhuo [73, 72] suggests that reducing the HbA1c cut-point for intervention from 6.0% to around 5.7% to 5.8% may be cost-effective but poses the dilemma of whether intervening at the lower threshold is feasible (given the cost additional burden to commissioners).

  There is also a number of research issues that may impact on the exact optimal cut-point for intervention :

- potentially different effectiveness of intervention according to baseline HbA1c level
- the impact of repeat risk assessment policies

- Switching to metformin is a cost-effective option for poor-responders to lifestyle intervention [4], assuming that metformin does not have a markedly reduced efficacy in poor-responders to lifestyle intervention compared to treatment-naïve patients. Similarly, discontinuing the lifestyle intervention would improve the cost-effectiveness of the intervention strategy for those who achieve no response to lifestyle intervention.

- Repeat risk assessment for diabetes every 3-5 years has been suggested.

4.7 Limitations of the analysis

4.7.1 Sensitivity Analyses and uncertainty

For one of the key parameters, treatment effectiveness in individuals identified with IGR through FPG or HbA1c tests, there was a lack of evidence, especially if cut-points for intervention result in higher baseline glucose levels than those in the large prevention trials. Given this, we adopted a conservative base case assumption of 70% of the effectiveness in patients with IGT (per Section 2.5.7.3).

It would have been useful to examine further whether the results and conclusions are sensitive to alternative assumptions around other model parameters. Unfortunately, this was not possible given time constraints.

4.7.2 Effectiveness of intervention at different baseline glucose levels

There is a lack of evidence on the impact of baseline glucose levels on the medium to long-term effectiveness of preventive interventions, i.e. is there any significant benefit from intervening at lower levels, e.g. an HbA1c of 5.7% rather than 6.0%. If so, there may be a significant impact on the relative cost-effectiveness on intervening at different levels.

4.7.3 Burden of Obesity

Reductions in weight through diet and exercise may have wider benefits than reduction in risk of diabetes and improvement in quality-of-life. Such weight-related co-morbidities, including obstructive sleep apnoea, polycystic ovarian syndrome and non-alcoholic fatty liver disease, amongst others are not captured well in diabetes models and there may be some underestimation of benefits of sustained lifestyle intervention.

4.8 Publication of final version of the Leicester Practice Database Score

The algorithm used in the economic analysis has subsequently been modified during academic peer review prior to publication. **Therefore, the identification of target individuals for glucose testing from GP practice data, including the choice of cut-point, should use the final published algorithm (Gray 2012 [1]).**

The risk factors included are age, gender, BMI, ethnicity, prescribed anti-hypertensives, and family history of diabetes.

4.9 Unanswered questions and future research

4.9.1 Re-screening interval

Time constraints, as well as concerns about gaps in the evidence base, precluded development of a robust model of re-screening. Based on existing published literature, a re-screening at 3 to 5 years may be reasonable. It has been reported that 60% of people who develop diabetes have either IGT or IFG 5 years or so before, with the other 40% having normal glucose tolerance at that time [24] – this suggests that re-screening more frequently than every 5 years may be necessary.

4.9.2 Possible Further Primary research

More research is needed to understand:

- how effective lifestyle interventions are in individuals identified as being at risk of diabetes using an HbA1c or FPG test
- the effectiveness of preventive interventions at different baseline glucose levels, e.g. does the effectiveness change with HbA1c levels close to the 6.5% threshold for diabetes ? Do interventions work as well from lower baseline HbA1c levels, e.g. 5.7%. Studies of sufficient duration are needed to demonstrate the true effect.
- the impact of switching to metformin in those that don't succeed with lifestyle intervention
- the potential role of telecare in supporting the delivery of prevention programs - one study suggested that a brief program followed by interactive technology support could help to increase the size of the weight loss among participants without increasing resource cost [74].

4.9.3 Possible Further Secondary research

It would be invaluable to understand how the degree of reduction in risk of diabetes through intervention varies across the range of glucose intolerance from borderline NGT/IGR through to onset of diabetes. This would help to define more clearly which individuals it is most cost-effective to intervene in.

It seems clear that better risk stratification of those identified with IGR is needed – a joint risk equation simultaneously showing the prognostic significance of a risk score alongside a glucose measure is needed as both have been shown to be highly predictive.

It is also necessary to understand what the optimal group size for preventive interventions is.

As HbA1c varies according to age and ethnicity, potentially alternative cut-points for intervention may be justifiable.

5. <u>APPENDICES</u>

<u>Appendix 1 : Sample search strategy for EconLit (via OVID SP)</u>

1   (risk assessment or screening or monitoring or diagnostic or diagnosis or glucose test or HBA1C).ti,ab.

2   (diabetes or pre-diabetes or pre-diabetes or IGT or impaired glucose tolerance or IFG or impaired fasting glucose or FPG or fasting plasma glucose).ti,ab.

3   1 and 2

4   limit 3 to yr="1998 -Current"

Appendix 2 : Health economic papers not included in the Economic Review of risk assessment plus prevention

Table 22 : Health economic papers 2005-2010 excluded from further review

Publication	Reason for exclusion from further assessment
Currie CJ, Peters JR, McEwan P. Evaluation of the clinical outcome and financial costs of delaying the onset of frank type-2 diabetes *Value in Health*, 2005 8 (3): 355	Abstract only. Only models impact of diabetes delay; no costs of risk assessment or intervention
Herman et al. The Cost-Effectiveness of Lifestyle Modification or Metformin in Preventing Type 2 Diabetes in adults with Impaired Glucose Tolerance *Ann Intern Med.* 2005;142:323-332.	Only considers cost-effectiveness of DPP intervention; no risk assessment costs or benefits from early diagnosis of diabetes included
Eddy et al. Clinical Outcomes and Cost-effectiveness of Strategies for Managing People at High Risk for Diabetes. *Ann Intern Med.* 2005;143:251-264.	Only considers cost-effectiveness of DPP intervention; no risk assessment costs or benefits from early diagnosis of diabetes included Note that Archimedes model has significantly different assumptions about natural history of diabetes in comparison to Herman et al and more recent models.
Viglen et al. Cost Effectiveness of Preventive Interventions in Type 2 Diabetes Mellitus A Systematic Literature Review *Pharmacoeconomics* 2006; 24 (5): 425-441	Only includes studies up to 2004. Only includes diabetes prevention in risk groups evidence from Segal (1998) and Palmer (2000)
Johnson et al. High-Risk Individuals' Willingness to Pay for Diabetes Risk-Reduction Programs *Diabetes Care* 29:1351–1356, 2006	Only examined willingness in pay for DPP intervention in largely obese US population at risk.
Ramachandran et al. Cost Effectiveness of the Interventions in the Primary Prevention of Diabetes among Asian Indians: Within trial results of the Indian Diabetes Prevention Programme (IDPP) *Diabetes Care* 2007;**30**:2548–2552.	Only considered cost of intervention per case prevented within RCT; no modelling of other costs or longer term benefits
Jacobs-Van der Bruggen MAM et al. Lifestyle interventions are cost-effective in people with different levels of diabetes risk. *Diabetes Care* 2007;30:128-134.	Intervention for general population and for obese population group – no risk assessment or intervention strategies targeted for pre-diabetes groups

Department of Health. Economic Modelling for Vascular Checks DH 2008. Consultation document.	Assumes NHS Vascular Checks Programme with use of FINDRISC followed by OGTT (based on screening strategies advised in The Handbook for Vascular Risk Assessment, Risk Reduction and Management NSC 2008.)Costs and benefits based on HTA Obesity review 2004;8(21) pp158 and HTA Diabetes Screening Review (Waugh et al 2007). Reports overall cost effectiveness of Vascular Checks programme.
Johansson P et al A cost-effectiveness analysis of a community-based diabetes program in Sweden. *Int J Tech Assess Health Care* 2009;25:350-358	Community level interventions for whole community – no risk assessment for pre-diabetes or diabetes or targeting of high risk groups
Neumann A. Assessing the Cost-Effectiveness of the Saxon Diabetes Type 2 Prevention Program Using a Markov Model. Thesis 2009	Unpublished Master's dissertation. Only considers cost-effectiveness of DPP and DPS interventions in a Swedish population; no risk assessment costs or benefits from early diagnosis of diabetes included
Zhuo. Progression from Pre-diabetes to Diabetes raises Healthcare Utilisation. *Payers Perspectives. American Health and Drug Benefits.* 2010 (3) 5: S4-5	Only considers healthcare costs associated with pre-diabetes and diabetes based on US insurance claims
Kahn et al. Age at initiation and frequency of screening to detect type 2 diabetes: a cost-effectiveness analysis.*Lancet* 2010;375:1365–1374	Only considers costs and benefits of earlier detection of Type 2 diabetes rather than of diabetes prevention in high risk populations.

Table 23 : Health economic papers only considering benefits from diabetes prevention (rather than prevention and earlier diagnosis)

	Population	Eligibility for intervention	Risk reduction intervention	Costs & outcomes included	Cost per QALY gained
Icks et al. Clinical and cost-effectiveness of primary prevention of Type 2 diabetes in a 'real world' routine healthcare setting: model based on the KORA Survey 2000 *Diabetic Medicine* 2007;24:473–480	60-74yrs in KORA survey population (Germany)	pre-DM and BMI>24	DPP lifestyle intervention & metformin	Costs of risk assessment and intervention; costs per case prevented	N/a Reported cost per case prevented over 3 years
Lindgren et al. Lifestyle intervention to prevent diabetes	Screened 60 year olds (Stockholm,	BMI>25 or	Finnish DPS	Costs of intervention only;	Euro/QALY

in men and women with impaired glucose tolerance is cost-effective International Journal of Technology Assessment in Health Care, 2007;23:177–183.	Sweden)	FBG >6.1 No DM	lifestyle modification	QALYs	2,363
Hoerger et al .Cost-effectiveness of screening for pre-diabetes among overweight and obese U.S. Adults *Diabetes Care* 2007;30:2874–287.	45-74 year olds with BMI>25 in US (NHANES)	1. IGT and IFG 2. IGT or IGF	DPP lifestyle modification	Risk assessment and intervention costs; QALYs	US$/QALY 1. $8,181 2. $9,511
Bertram et al. Assessing the cost-effectiveness of drug and lifestyle intervention following opportunistic screening for pre-diabetes in primary care *Diabetologia* 2010; 53:875–881	Opportunistic screening if>55 years or >45 years plus high BMI, FH, HT; aboriginal; GDM (Australia)	"pre-diabetes" i.e. IGT or IGF?	1. acarbose 2. metformin 3.orlistat 4.diet 5.exercise 6.diet + exercise	Costs of intervention only; DALYs	AU$/DALY 1. 37,000 2. 22,000 3. 100,000 4. 38,000 5. 30,000 6. 23,000

Appendix 3 : South Asians aged 25-39 - Comparison of the Leicester Practice Database Score versus BMI >23 as the criteria for proceeding to a glucose test

Concerns were raised within the PDG during final discussions that the LPDS might not work as well for people of age 25-39 age as for older people because age is such an important factor in the risk score. As the score was not calibrated to this age group, there was concern that people might be falsely reassured because generally their scores could be relatively low.

Although too late to repeat the modelling using BMI>23 at the criteria, it was considered a useful analysis for the PDG to compare the prevalence of T2DM/IGR for South Asians meeting the LPDS risk score cut-point versus BMI >23 in the LEADER dataset .

Definitions/Criteria :
Type 2 diabetes : HbA1c >=6.5%
IGR : HbA1c >=6.0% and <6.5%

The comparison is undertaken using 2 alternative cut-points for the LPDS, a) ≥ 5.25 and b) ≥ 4.75

a) Using LPDS cut-point ≥ 5.25

Pre-screen	N				Prevalence		
	Total	T2DM	IGR	NGT	T2DM	IGR	NGT
LPDS ≥ 5.25	223	14	30	179	6.3%	13.5%	80.3%
BMI >23	370	18	43	309	4.9%	11.6%	83.5%

The above results suggest that, compared to a cut-point of >=5.25, choosing to use BMI>23 rather than LPDS as a pre-screen has the following effects –

- a lot more individuals go on to blood glucose testing
- more individuals in absolute terms would be identified with IGR/diabetes
- there is a trend towards a lower prevalence of T2DM and IGR but it is likely that screening is still cost-effective using BMI as a pre-screen in 25-39 year old South Asians
- this suggests that, if data is available on GP databases to calculate the risk score, this is more efficient than using BMI alone, at this cut-point

b) Using LPDS cut-point ≥ 4.75

Pre-screen	N				Prevalence		
	Total	T2DM	IGR	NGT	T2DM	IGR	NGT
LPDS ≥ 4.75	407	18	46	343	4.4%	11.3%	84.3%
BMI >23	370	18	43	309	4.9%	11.6%	83.5%

Comparing BMI>23 to a lower LPDS cutpoint, >=4.75, results in an almost identical prevalence and similar

numbers going on to glucose testing and diagnosis as IGR/T2DM. In this case, BMI alone might be the better pre-screening option.

Appendix 4 : Notes on sensitivity etc

Table 24 : example of test performance

	Disease present ?		
		+	-
Test Outcomes	+	95 TP	90 FP
	-	5 FN	810 TN
1000 patients			

For any given test, it is important to know what proportion of tests yield true positive (TP), false positive (FP), true negative (TN) and false negative (FN) diagnoses. These are used to calculate the sensitivity, specificity, positive predictive value, and negative predictive value, in order to give measures of how useful the test is to detect a disease or characteristic in the given population. We would want to know:

- How likely is the test to detect the presence of a characteristic in someone with the characteristic? [sensitivity = TP / (TP+FN) = 95/(95+5) = 95%]

- How likely is the test to detect the absence of a characteristic in someone without the characteristic? [Specificity = TN / (FP+TN) = 810/(90+810) = 90%]

- How likely is someone with a positive test result to actually have the characteristic? [Positive predictive value = TP / (TP+FP) = 95/(95+90) =51%] This depends upon the prevalence of the characteristic in the given population

- How likely is someone with a negative test result to actually not have the characteristic ? [Negative predictive value = TN / (TN+FN) = 810/(810+5) = 99%] This also depends upon the prevalence of the characteristic in the given population

A good test has the following attributes -

Sensitivity - high so identify majority of cases of IGR/diabetes

Positive predictive value - high so not identifying lots of individuals without IGR/diabetes

Specificity - high so that do not identify lots of false positives

Note, however, that if the sensitivity of a test improves, it is at the expense of a lower specificity. The converse is also the case.

Appendix 5 : Inflation adjustments

Inflation

Year	Index	Adj vs prev year	
2005/06	240.9		
2006/07	249.8		
2007/08	257.0	1.029	
2008/09	267.0	1.039	
2009/10	271.5	1.017	
2010/11		1.017	assumption - pay freeze in public sector means probably low
2011/12		1.017	assumption - pay freeze in public sector means probably low
Overall adjustment for 2011/12 versus 2006/7		1.124	

Figures up to 2009/10 from Curtis [45]

Appendix 6 : Description of Treatment of Diabetes Model

Metabolic natural history

Glucose levels :

Type 2 diabetes is diagnosed when a plasma glucose concentration or oral glucose tolerance test yields results above a 'normal' threshold, reflecting an impaired ability to regulate blood glucose levels. The simulation model is for use in patients either newly diagnosed or post-diagnosis. Long-term glycaemic control is best measured using hemoglobin (HbA1c) as this reflects average levels over a 3-month period. Uncontrolled rising glucose levels lead to hyperglycaemia. Sustained hyperglycaemia causes tissue damage and increases the risk of microvascular complications (retinopathy, neuropathy and nephropathy), which will already be present in a minority of newly- diagnosed patients. Hyperglycaemia also leads to an

increased risk of the more serious macrovascular complications (stroke and coronary events), particularly when hypertension and/or hypercholesterolemia are present.

Other metabolic disorders :

Elevated glucose levels are frequently accompanied by other elements of the metabolic syndrome (a clustering of several abnormal metabolic variables), the most well-understood of which are blood pressure and lipid levels. We have modelled these using systolic blood pressure and total cholesterol respectively. Abnormal levels of these two are risk factors for developing complications, and a particularly significant in cardiovascular disease (CHD and stroke). Correction of these 2 metabolic imbalances is as important as glycaemic control (of HbA1c) for controlling the risk of complications.

Total cholesterol (TC) is made up of the following –

- LDL-cholesterol ('bad' cholesterol)
- HDL-cholesterol ('good' cholesterol)
- Triglycerides

We have only modelled TC and HDL because these two components are the factors which were significant in the UKPDS CVD risk engines (see 3.3.1 & 3.3.2). Although Triglycerides are implicated as possibly having an independent role in CVD risk, there is no quantified consensus on their independent effect with respect to TC and HDL. The relationship between TC and the components is covered by the Friedwald formula (we have not included the formula as there are different versions according to measurement scale).

Any economic evaluation of antiglycaemic therapies must stipulate an appropriate level of control of co-existing metabolic imbalances as this will have a scaling effect on any incremental differences between the therapies on glycaemic control

State Transition Methodology for simulating risk of incidence/progression of comorbidities

Markov models are employed to describe disease progression in a situation where a patient is deemed to have a repeated probability or risk of moving from their current health state to the next state for any given period. A variation, known as state-transition models, incorporate time as a determining factor for the level of risk. Most of our sub-models also incorporate updated metabolic factors as determinants of risk. The sub-models run in parallel, allowing patients to develop more than one complication simultaneously in any period. The sub-models represent a situation of "competing risk" in which survival benefits arising from one intervention to reduce complication A may be partly offset by increased incidence of complication B.

The model can now simulate disease progression at shorter intervals than 1 year. The Scenario sheet is set up so can only select 1, 2 or 4 periods per year

Cardiovascular (CVD) Risk models

These are the most important risk modules as the excess CVD rates represent the greatest health burden arising from diabetes.

The CVD equations are based largely on the UKPDS study of newly diagnosed Type 2 diabetes patients (UKPDS56, 60 & 66).

Coronary heart disease is the most serious complication of diabetes with a much greater risk than that of the general population. The CHD model is driven by –

- the 3 modifiable metabolic risk factors – HbA1c, blood pressure and total cholesterol. The method for on-going risk adjustments according to modification of these risk factors is discussed below
- other patient characteristics such as age, ethnicity

The possible outcomes included are rates of –

- first CHD event (MI, sudden death, unstable angina) split into non-fatal and fatal subsequent events split into non-fatal and fatal

Microvascular Risk Equations

Retinopathy :

Risks are from Eastman [55] using incidence rates from various studies. We have assumed that these rates apply to 'standard care' with a corresponding HbA1x level of 10% as observed in the most prominent of these studies, the Wisconsin Epidemiologic Study of Diabetic Retinopathy (WESDR) [75] which had an average HbA1c of 10%. The DCCT [76] was used by Eastman [56] to provide equations relating risk to the degree of glycaemic control (measured by an average HbA1c assumed constant for life).

Our microvascular sub-models therefore calculate risk based on the mean updated HbA1c) compared to a constant level of 10%.

Nephropathy :

Nephropathy is the most important microvascular sub-model.
This sub-model covers progression from no disease through microalbuminuria, proteinuria and through four end-stage renal disease states (Haemodialysis, Peritoneal dialysis, transplantation [return to no nephropathy] and death from nephropathy).

Development of Microalbuminuria through to Gross Proteinuria
Microalbuminuria is defined in the Wisconsin Epidemiologic Study of Diabetic Retinopathy (WESDR) [77] as defined as > or = 0.03 g/L but < 0.3 g/L. An alternative definition is a Urinary Albumin Excretion (UAE) rate between 30 to 300 mg/24 hr (or 20 to 200 µg/min) [78]. Macroalbuminuria is present if UAE >300 mg/24 hr. HbA1c is the main driver in the early stages of the disease. The HbA1c-related hazard rates are from Eastman [56] based on the WESDR and the DCCT.**Error! Bookmark not defined.**

Ethnicity affects risk of developing microalbuminuria and this is incorporated into the Eastman risk equations.

No screening for microalbuminuria is assumed, although this is an area in debate and is carried out by some clinicians.
Progression to the stage of Gross Proteinuria (GPR) also from Eastman is based on the Rochester Epidemiology Project [79] and the DCCT. Blood pressure is also implicated in much of the literature[80] as a risk factor for development of these states.

Progression of kidney disease
In the work by Eastman [56], HbA1c was not a risk factor for progression from GPR towards end-stage renal disease. Recent literature repeatedly notes the influence of blood pressure on nephropathy progression

however. A recent meta-analysis clearly shows the importance of blood pressure once protein levels reach a certain point.

Stepwise therapy strategies

Any strategy can be input to a model provided the required parameters such as HbA1c change are available from evidence.

Discontinuation from therapy & adherence

The model takes account of sub-optimal adherence to antiglycaemic and lipid therapy in terms of control of risk factors.

Appendix 7 : Interim Results tables

For the interim results presented in Table 25 to

Table 28 below, the pathways and prognosis for the majority of the screened cohort were being determined according to an arbitrary strategy-specific glucose cut-point to separate cases of normal glucose tolerance and IGR. This limited their usefulness beyond comparing the cost-effectiveness of alternative intensities of intervention (see section 3.2.2).

The following take account of the cost of risk assessment as well as long-term costs and QALYs arising from subsequent treatment pathways.

Table 25 : Cost-effectiveness versus Vascular Checks algorithm with no intervention

Intervention	Incremental Costs (£)	Incremental QALYs	Net Benefit	Comment
Intensive intervention with intensive maintenance	- £ 54	0.0007	>0	Intensive intervention cost-effective versus no intervention (and dominates)

Table 26 : Cost-effectiveness of risk assessment with LPDS ≥ 4.75 points, HbA1c ≥ 5.7%

Results are shown compared to a low intensity intervention with low maintenance

Intervention	Incremental Costs (£)	Incremental QALYs	Net Benefit	Comment
Moderate intervention with moderate maintenance	£ 20	0.0029	>0	Moderate intervention cost-effective versus low intensity intervention
Intensive intervention with intensive maintenance	- £ 54	0.0007	>0	Intensive intervention cost-effective versus low intensity (and dominates)intervention

Table 27 : Cost-effectiveness of risk assessment with LPDS ≥ 5.0 points, HbA1c ≥ 5.85%

Results are shown compared to a low intensity intervention with low maintenance

Intervention	Incremental Costs (£)	Incremental QALYs	Net Benefit	Comment
Moderate intervention with moderate maintenance	- £ 11	0.0025	>0	Moderate intervention cost-effective versus low intensity intervention (and dominates)
Intensive intervention with intensive maintenance	- £ 3	0.0042	>0	Intensive intervention cost-effective versus low intensity intervention (and dominates)

Table 28 : Cost-effectiveness of risk assessment with LPDS ≥ 5.25 points, HbA1c ≥ 6.0%

Results are shown compared to a low intensity intervention with low maintenance

Intervention	Incremental Costs (£)	Incremental QALYs	Net Benefit	Comment
Moderate intervention with moderate maintenance	£ 0	0.0021	>0	Moderate intervention cost-effective versus low intensity intervention
Intensive intervention with intensive maintenance	- £ 1	0.0034	>0	Intensive intervention cost-effective versus low intensity intervention (and dominates)

Table 29 : Cost-effectiveness of risk assessment with LPDS ≥ 5.25 points, FPG ≥ 5.5%

Results are shown compared to a low intensity intervention with low maintenance

Intervention	Incremental Costs (£)	Incremental QALYs	Net Benefit	Comment
Moderate intervention with moderate maintenance	- £ 17	0.0035	>0	Moderate intervention cost-effective versus low intensity (and dominates) intervention
Intensive intervention with intensive maintenance	- £ 2	0.0045	>0	Intensive intervention cost-effective versus low intensity intervention (and dominates)

The incremental costs and QALYs between alternative strategies are, as is usual for diabetes-related lifestyle interventions, both small. This can make results sensitive to key assumptions and estimates.

6. <u>References</u>

(1) Gray L, Davies M, Hiles S, Taub N, Webb D, Srinivasan B et al. Detection of impaired glucose regulation and/or type 2 diabetes mellitus, using primary care electronic data, in a multiethnic UK community setting. *Diabetologia* 2012; 55(4):959-966.

(2) Karnon J, Goyder E, Tappenden P, McPhie S, Towers I, Brazier J et al. A review and critique of modelling in prioritising and designing screening programmes. *Health Technol Assess* 2007; 11(52):1-145.

(3) Waugh N, Scotland G, Gillett M, Brennan A, Goyder E, Williams R et al. Screening for type 2 diabetes: literature review and economic modelling. *Health Technology Assessment* 2007.

(4) Gillett M, Royle P, Snaith A, et al. Non-pharmacological interventions to reduce the risk of diabetes in people with impaired glucose regulation: systematic review and economic evaluation. *HTA Technology Assessment* 2012; Publication due August 2012 (details at www.hta.ac.uk/1541).

(5) Lauritzen T, Borch JK, Sandbaek A. Is prevention of type-2 diabetes feasible and efficient in primary care? A systematic PubMed review (Brief record). *Primary Care Diabetes* 2007; 1:5-11.

(6) Herman WH, Thomas MP, Hoerger TJ, Brandle M, Hicks K, Sorensen S et al. The cost-effectiveness of lifestyle modification or metformin in preventing Type 2 diabetes in adults with impaired glucose tolerance (Structured abstract). *Annals of Internal Medicine* 2005; 142:323-332.

(7) Eddy DM, Schlessinger L, Kahn R. Clinical outcomes and cost-effectiveness of strategies for managing people at high risk for diabetes (Structured abstract). *Annals of Internal Medicine* 2005; 143:251-264.

(8) Gillies CL, Lambert PC, Abrams KR, Sutton AJ, Cooper NJ, Hsu RT et al. Different strategies for screening and prevention of type 2 diabetes in adults: cost effectlveness analysis (Structured abstract). *BMJ* 2008; 336:1180-1185.

(9) Colagiuri S, Walker AE. Using an economic model of diabetes to evaluate prevention and care strategies in Australia (Structured abstract). *Health Affairs* 2008; 27:256-268.

(10) Chatterjee R, Venkat Narayan KM, Lipscomb J, Phillips LS. Screening Adults for Pre-Diabetes and Diabetes May Be Cost-Saving. *Diabetes Care* 2010; 33(7):1484.

(11) Schaufler TM. Cost Effectiveness of Preventive Screening Programmes for Type 2 Diabetes Mellitus in Germany. *Applied Health Economics and Health Policy* 191; . 8(3).

(12) Lindeman RD, Yau CL, Baumgartner RN, Morley JE, Garry PJ. Longitudinal study of fasting serum glucose concentrations in healthy elderly. The New Mexico Aging Process Study. *The journal of nutrition, health & aging* 2003; 7(3):172.

(13) Kahn R, Alperin P, Eddy D, Borch-Johnsen K, Buse J, Feigelman J et al. Age at initiation and frequency of screening to detect type 2 diabetes: a cost-effectiveness analysis. *The Lancet* 2010; 375(9723):1365-1374.

(14) Johnson SL, Tabaei BP, Herman WH. The efficacy and cost of alternative strategies for systematic screening for type 2 diabetes in the US population 45û74 years of age. *Diabetes Care* 2005; 28(2):307.

(15) Kuo HS, Chang HJ, Chou P, Teng L, Chen TH. A Markov chain model to assess the efficacy of screening for non-insulin dependent diabetes mellitus (NIDDM). *International journal of epidemiology* 1999; 28(2):233.

(16) Park PJ, Griffin SJ, Duffy SW, Wareham NJ. The effect of varying the screening interval on false positives and duration of undiagnosed disease in a screening programme for type 2 diabetes. *Journal of Medical Screening* 2000; 7(2):91.

(17) Scottish Public Health Network (ScotPHN). Updating the Scottish Needs Assessment Programme Report on Type 2 Diabetes: Screening and Prevention. 2010.

(18) Takahashi O, Farmer AJ, Shimbo T, Fukui T, Glasziou PP. HbA1c to Detect Diabetes Mellitus in Healthy Adults: When Should We Re-check? *Diabetes Care* 2010.

(19) Nichols GA, Hillier TA, Brown JB. Progression from newly acquired impaired fasting glusose to type 2 diabetes. *Diabetes Care* 2007; 30(2):228.

(20) Ackermann RT, Marrero DG, Hicks KA, Hoerger TJ, Sorensen S, Zhang P et al. An evaluation of cost sharing to finance a diet and physical activity intervention to prevent diabetes. *Diabetes Care* 2006; 29:1237-1241.

(21) Tuomilehto J, Lindström J, Eriksson J, Valle T, Hämäläinen H, Ilanne-Parikka P et al. Prevention of type 2 diabetes mellitus by changes in lifestyle among subjects with impaired glucose tolerance. *New England Journal of Medicine* 2001; 344(18):1343-1350.

(22) Hughes KAW. 11-Beta-hydroxysteroid dehydrogenase type 1 (11beta-HSD1) inhibitors in type 2 diabetes mellitus and obesity. *Expert Opinion on Investigational Drugs* 2008; 17(4):Apr.

(23) Holman N, Forouhi NG, Goyder E, Wild SH. The Association of Public Health Observatories (APHO) Diabetes Prevalence Model: estimates of total diabetes prevalence for England, 2010-2030. *Diabet Med* 2011.

(24) Unwin N, Shaw J, Zimmet P, Alberti K. Impaired glucose tolerance and impaired fasting glycaemia: the current status on definition and intervention. *Diabet Med* 2002; 19(9):708-723.

(25) Mostafa SA, Khunti K, Srinivasan BT, Webb D, Gray LJ, Davies MJ. The potential impact and optimal cut-points of using glycated haemoglobin, HbA1c, to detect people with impaired glucose regulation in a UK multi-ethnic cohort. *Diabetes research and clinical practice* 2010; 90(1):100-108.

(26) Saaristo et al. Cross-sectional evaluation of the Finnish Diabetes Risk Score: a tool to identify undetected type 2 diabetes, abnormal glucose tolerance and metabolic syndrome. *Diabetes and Vascular Disease Research* 2005;67-72.

(27) World Health organisation. Use of Glycated Haemooglobin (HbA1c) in the Diagnosis of Diabetes Mellitus – Abbreviated Report of a WHO Consultation . 2011.

(28) Park PJ, Griffin SJ, Sargeant L, Wareham NJ. The performance of a risk score in predicting undiagnosed hyperglycemia. *Diabetes Care* 2002; 25(6):984.

(29)   Gray LJ, Taub NA, Khunti K, Gardiner E, Hiles S, Webb DR et al. The Leicester risk assessment score for detecting undiagnosed type 2 diabetes and impaired glucose regulation for use in a multiethnic UK setting. *Diabetic Medicine* 2010; 27(8):887-895.

(30)   Agodoa LY, Appel L, Bakris GL, Beck G, Bourgoignie J, Briggs JP et al. Effect of ramipril vs amlodipine on renal outcomes in hypertensive nephrosclerosis. *JAMA: the journal of the American Medical Association* 2001; 285(21):2719.

(31)   World Health Organization. Definition, diagnosis and classification of diabetes mellitus and its complications: Report of a WHO Consultation. Part 1. Diagnosis and classification of diabetes mellitus. *Geneva, World Health Organization* 1999.

(32)   Department of Health. Economic Modelling for Vascular Checks - A Technical Consultation. 2008.

(33)   Christensen DL, Witte DR, Kaduka L, Jørgensen ME, Borch-Johnsen K, Mohan V et al. Moving to an A1C-based diagnosis of diabetes has a different impact on prevalence in different ethnic groups. *Diabetes Care* 2010; 33(3):580.

(34)   Bonora E, Kiechl S, Mayr A, Zoppini G, Targher G, Bonadonna RC et al. High-Normal HbA1c Is a Strong Predictor of Type 2 Diabetes in the General Population. *Diabetes Care* 2011; 34(4):1038.

(35)   Holman RR, Blackwell L, Stratton IM, Manley SE, Tucker L, Frighi V. Six-year results from the Early Diabetes Intervention Trial. *Diabet Med* 2003; 20(Suppl 2):S15.

(36)   Lindström J, Ilanne-Parikka P, Peltonen M, Aunola S, Eriksson JG, Hemi÷ K et al. Sustained reduction in the incidence of type 2 diabetes by lifestyle intervention: follow-up of the Finnish Diabetes Prevention Study. *The Lancet* 2006; 368(9548):1673-1679.

(37)   Hamman RF, Wing RR, Edelstein SL, Lachin JM, Bray GA, Delahanty L et al. Effect of weight loss with lifestyle intervention on risk of diabetes. *Diabetes Care* 2006; 29(9):2102.

(38)   Saaristo T, Moilanen L, Korpi-Hyovalti E, Vanhala M, Saltevo J, Niskanen L et al. Lifestyle Intervention for Prevention of Type 2 Diabetes in Primary Health Care. *Diabetes Care* 2010; 33(10):2146.

(39)   Meigs JB, Muller DC, Nathan DM, Blake DR, Andres R. The natural history of progression from normal glucose tolerance to type 2 diabetes in the Baltimore Longitudinal Study of Aging. *Diabetes* 2003; 52(6):1475.

(40)   Gillett M, Dallosso HM, Dixon S, Brennan A, Carey ME, Campbell MJ et al. Delivering the diabetes education and self management for ongoing and newly diagnosed (DESMOND) programme for people with newly diagnosed type 2 diabetes: cost effectiveness analysis. *BMJ: British Medical Journal* 2010; 341.

(41)   Bray GA, Chatellier A, Duncan C, Greenway FL, Levy E, Ryan DH et al. 10-Year follow-up of diabetes incidence and weight loss in the Diabetes Prevention Program Outcomes Study. *Lancet* 2009; 374(9702):1677-1686.

(42)   Ashcroft JS. Prevention of diabetes: Lifestyle and metformin are the way forward. *BMJ: British Medical Journal* 2006; 333(7574):918.

(43)   Lindgren P, Lindström J, Tuomilehto J, Uusitupa M, Peltonen M, J÷nsson B et al. Lifestyle intervention to prevent diabetes in men and women with impaired glucose tolerance is cost-effective. *International Journal of Technology Assessment in Health Care* 2007; 23(02):177-183.

(44) Irvine L, Barton GR, Gasper AV, Murray N, Clark A, Scarpello T et al. Cost-effectiveness of a lifestyle intervention in preventing Type 2 diabetes. *Int J Technol Assess Health Care* 2011; 27(4):275-282.

(45) Curtis. Unit Costs of Health and Social Care 2010. *Personal Social Services Research Unit (PSSRU)* 2010.

(46) Almeida F, Shetterly S, Smith-Ray R, Estabrooks P. Reach and effectiveness of a weight loss intervention in patients with pre-diabetes in Colorado. *Preventing Chronic Disease* 2010; 7(5):A103.

(47) Laaksonen D, Lindström J, Lakka T, Eriksson J, Niskanen L, Wikström K et al. Physical activity in the prevention of type 2 diabetes: the Finnish diabetes prevention study. *Diabetes* 2005; 54(1):158-165.

(48) Li G, Zhang P, Wang J, Gregg E, Yang W, Gong Q et al. The long-term effect of lifestyle interventions to prevent diabetes in the China Da Qing Diabetes Prevention Study: a 20-year follow-up study. *Lancet* 2008; 371(9626):1783-1789.

(49) Pajunen P, Peltonen M, Eriksson JG, Ilanne Parikka P, Aunola S, Keinänen-Kiukaanniemi S et al. HbA1c in diagnosing and predicting Type 2 diabetes in impaired glucose tolerance: the Finnish Diabetes Prevention Study. *Diabet Med* 2011; 28(1):36-42.

(50) Forouhi NG, Luan J, Hennings S, Wareham NJ. Incidence of Type 2 diabetes in England and its association with baseline impaired fasting glucose: the Ely study 1990û2000. *Diabet Med* 2007; 24(2):200-207.

(51) Ratner R, Goldberg R, Haffner S, Marcovina S, Orchard T, Fowler S et al. Impact of intensive lifestyle and metformin therapy on cardiovascular disease risk factors in the diabetes prevention program. *Diabetes Care* 2005; 28(4):888-894.

(52) Lindström J, Peltonen M, Eriksson J, Aunola S, Hämäläinen H, Ilanne-Parikka P et al. Determinants for the effectiveness of lifestyle intervention in the Finnish Diabetes Prevention Study. *Diabetes Care* 2008; 31(5):857-862.

(53) Bonora E, Kiechl S, Mayr A, Zoppini G, Targher G, Bonadonna RC et al. High-Normal HbA1c Is a Strong Predictor of Type 2 Diabetes in the General Population. *Diabetes Care* 2011; 34(4):1038.

(54) Selvin. Predicting Diabetes Using the Fasting Glucose, A1c, or OGTT. *Diabetes Care* 2010.

(55) Eastman RC, Javitt JC, Herman WH, Dasbach EJ, Zbrozek AS, Dong F et al. Model of complications of NIDDM. I. Model construction and assumptions. *Diabetes Care* 1997; 20(5):725.

(56) Eastman RC, Javitt JC, Herman WH, Dasbach EJ, Copley-Merriman C, Maier W et al. Model of complications of NIDDM. II. Analysis of the health benefits and cost-effectiveness of treating NIDDM with the goal of normoglycemia. *Diabetes Care* 1997; 20(5):735.

(57) Stevens RJ, Kothari V, Adler AI, Stratton IM, Holman RR. The UKPDS risk engine: a model for the risk of coronary heart disease in Type II diabetes (UKPDS 56). *Clinical Science* 2001; 101(6):671-679.

(58) Kothari V, Stevens RJ, Adler AI, Stratton IM, Manley SE, Neil HA et al. Risk of stroke in type 2 diabetes estimated by the UK Prospective Diabetes Study risk engine (UKPDS 60). *Stroke* 2002; 33:1776-1781.

(59) British National Formulary (BNF 58) accessed December 2009 at http://bnf.org/bnf/.

(60) Belcher G, Lambert C, Edwards G, Urquhart R, Matthews DR. Safety and tolerability of pioglitazone, metformin, and gliclazide in the treatment of type 2 diabetes. *Diabetes research and clinical practice* 2005; 70(1):53-62.

(61) Dennett SL, Boye KS, Yurgin NR. The impact of body weight on patient utilities with or without type 2 diabetes: a review of the medical literature. *Value in Health* 2008; 11(3):478-486.

(62) Warren E, Brennan A, Akehurst R. Cost-effectiveness of sibutramine in the treatment of obesity. *Medical Decision Making* 2004; 24(1):9.

(63) O'Meara S, Riemsma R, Shirran L, Mather L, Ter Riet G. The clinical effectiveness and cost-effectiveness of sibutramine in the management of obesity: a technology assessment. *Health Technology Assessment (Winchester, England)* 2002; 6(6):1.

(64) NICE clinical guideline 67. Lipid modification: Cardiovascular risk assessment and the modification of blood lipids for the primary and secondary prevention of cardiovascular disease. May 2008 (reissued March 2010).

(65) Gray L, Tringham J, Davies M, Webb D, Jarvis J, Skinner T et al. Screening for type 2 diabetes in a multiethnic setting using known risk factors to identify those at high risk: a cross-sectional study. *Vasc Health Risk Manag* 2010;(6):837-842.

(66) Boyko J, Gerstein H, Mohan V, Yusuf S, Sheridan P, Anand S et al. Effects of ethnicity on diabetes incidence and prevention: results of the Diabetes REduction Assessment with ramipril and rosiglitazone Medication (DREAM) trial. *Diabet Med* 2010; 27(11):1226-1332.

(67) Srinivasan ea. Progression from Impaired Glucose Metabolism (IGM) to Type 2 Diabetes Mellitus (T2DM) - Prospective Data from a UK Screening Study. ADA 69th Scientific Sessions (2009) Poster Abstract 1033-P. *Diabetes* 2009.

(68) Crandall J, Schade D, Ma Y, Fujimoto WY, Barrett-Connor E, Fowler S et al. The influence of age on the effects of lifestyle modification and metformin in prevention of diabetes. *J Gerontol A Biol Sci Med Sci* 2006; 61(10):1075-1081.

(69) Petersen S, Peto V, Rayner M. Coronary heart disease statistics. 2004. British Heart Foundation Health Promotion Research Group; British Heart Foundation.London.

(70) Retnakaran R, Cull CA, Thorne KI, Adler AI, Holman RR, UKPDS Study Group. Risk Factors for Renal Dysfunction in Type 2 Diabetes. U.K. Prospective Diabetes Study 74. *Diabetes* 2006; 55(6):1832-1839.

(71) Fleischmann E, Teal N, Dudley J, May W, Bower JD, Salahudeen AK. Influence of excess weight on mortality and hospital stay in 1346 hemodialysis patients. *Kidney Int* 1999; 55(4):1560-1567.

(72) Zhuo X, Zhang P, Selvin E, Hoerger TJ, Ackermann RT, Li R et al. Alternative HbA1c Cutoffs to Identify High-Risk Adults for Diabetes Prevention: A Cost-Effectiveness Perspective. *Am J Prev Med* 2012; 42(4):374-381.

(73) Zhuo X, Zhang P, Selvin E, Ackermann R, Li R, Gregg E. An Economic Analysis of Optimal A1c Cutpoints To Define Pre-DM. *Poster presented at 70th ADA Scientific Sessions 2010, Published in Diabetes 2010;59(suppl 1):abstract 0199-OR* 2010.

(74) Estabrooks PA, Smith-Ray RL. Piloting a behavioral intervention delivered through interactive voice response telephone messages to promote weight loss in a pre-diabetic population. *Patient Education and Counseling* 2008; 72(1):34-41.

(75)   Klein R. Hyperglycamia and microvascular and macrovascular disease in diabetes. *Diabetes Care* 1995; 18:258-268.

(76)   The Diabetes Control and Complications Trial Research Group. The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus. *N Engl J Med* 1993; 329(14):977-986.

(77)   Klein R, Klein BE, Moss SE. Prevalence of microalbuminuria in older-onset diabetes. *Diabetes Care* 1993; 16(10):1325.

(78)   Critchley JA, Zhao HL, Tomlinson B, Leung W, Thomas GN, Chan JCN et al. Management of nephropathy in patients with type 2 diabetes. *Chinese medical journal* 2002; 115(1):129-135.

(79)   Ballard DJ, Humphrey LL, Melton LJ, Frohnert PP, Chu PC, O'fallon WM et al. Epidemiology of persistent proteinuria in type II diabetes mellitus. Population-based study in Rochester, Minnesota. *Diabetes* 1988; 37(4):405.

(80)   UK National Electronic Library for Health. Clinical Guidelines for Type 2 Diabetes : Renal Disease-prevention and early management. 2011.