GLOW: Evaluation of the medium to long term impact of a tailored diabetes education and behavioural weight management programme versus diabetes education

Project Team

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1. Purpose of the Health Economic and Decision Modelling Analysis Plan

This Health Economic and Decision Modelling Analysis Plan (HEDMAP) sets out the protocol for the health economic analysis of the GLoW trial. This analysis plan should be read in conjunction with the trial protocol and the Within Trial Health Economics Analysis Plan (WT HEAP).

2. Background

In the UK, individuals diagnosed with type-2 diabetes can access diabetes education services from the NHS via referral to DESMOND as recommended in clinical guidelines. DESMOND is the acronym for Diabetes Education and Self Management for Ongoing and Newly Diagnosed. DESMOND is a structured group diabetes education (DE) programme designed to increase an individual's knowledge of type 2 diabetes but also encourage them to develop the skills to help effectively self-manage the condition. It is part of a school of patient education for people with diabetes, developed by a number of NHS Organisations. A new intervention combining WW classes and NICE compliant Diabetes education (DE) has been developed. However, this new programme is unlikely to be widely commissioned without robust evidence of cost-effectiveness. The GLoW trial will provide reliable evidence on the relative effectiveness and cost-effectiveness of a tailored diabetes education and behavioural weight management programme (DEW) versus DE, for people with a diagnosis of type-2 diabetes in the last 3 years.

2.1. The decision problem

2.1.1. Aims

The aim of the health economic evaluation is to estimate whether a tailored diabetes education and behavioural weight management programme is cost-effective from a UK NHS and personal social services perspective compared with usual care.

2.1.2. Objectives

The objectives of the GLoW health economics decision modelling analysis are:

I. To estimate the average change in weight, BMI and HbA1c for participants after 12 months for the intervention arms compared with the comparator.
II. To implement estimated metabolic trajectories into the SPHR Diabetes Treatment Model to estimate the long-term health impact of changes across a lifetime horizon.
III. To estimate the incremental diabetes related complications, life years and quality adjusted life years of the intervention arms compared with the comparator.
IV. To estimate the incremental costs of the intervention arms over a lifetime compared with the comparator.

2.1.3. Interventions

A tailored diabetes education and behavioural weight management programme (DEW).

2.1.4. Comparators

Usual care, including referral to DESMOND.

2.1.5. Population and relevant subgroups

The population in the analyses will match the eligibility criteria for the main trial (1), which are:

Inclusion

- Body mass index≥25kg/m2 .
- Age≥18 years.
- Diagnosis of T2D within the previous 36 months (confirmatory blood test will not be required).
- Capable of giving informed consent.
- Have a good understanding of the English language (study materials are not tailored to support nonEnglish language speakers).
- Willing to be randomised.
- Willing to attend follow-up visits at a local participating general practitioner (GP) practice or research centre.

Exclusion

- Using insulin.
- Previous/planned bariatric surgery.
- Current/planned pregnancy.
- Current diagnosis of eating disorder.
- Already received a structured DE programme.
- GP considers unsuitable.
- Participation in another structured behaviour change programme for diet and/or physical activity within the past 3 months.

3. Economic analysis

3.1. Type of Economic evaluation used

Two types of economic evaluation will be conducted, one lifetime horizon model-based analysis, which will extrapolate relevant clinical data from the GLoW trial data and one analysis of the resource use and EQ-5D-5L data collected in the GLoW data over a one year time horizon. This document relates to the analyses planned for the first analysis.

The model-based analysis is needed for two key reasons:

- Firstly, the NICE reference case specifies that the time horizon of economic analyses are "Long enough to reflect all important differences in costs or outcomes between the

technologies being compared" (2). The lifetime horizon of the model-based analysis is in line with this recommendation, whereas the one-year time horizon of the GLoW trial is unlikely to capture all of these important differences between the study arms.

- Secondly, it is expected that GLoW participants will develop non-communicable diseases beyond the follow-up of the trial. It is unlikely that the trial is powered to detect differences in key outcome such as cardiovascular disease within 1 year. Therefore, modelling is needed to extrapolate the benefits of the short-term outcomes on long-term health and cost consequences.

3.2. The Health Economic Decision Modelling Analysis Plan

3.2.1. Perspective

All analyses will take an NHS and personal social services perspective, in line with current NICE guidance (2).

3.2.2. Cost of the intervention

A detailed costing for both the DEW intervention and DE comparator will be conducted. As part of this components of the intervention that are commissioned from existing services, will be costed at the commissioned price. These will be sought from the providers. The cost of the intervention will include the cost to deliver the components of the DEW and DE intervention and will include the costs associated with referrals to other weight management providers.

The cost of the intervention may vary according to whether it is delivered in person or online. In the base case analysis we will weight the cost estimate on the proportion of participants in the trial receiving the in person or online programme. We will test this assumption with scenario analyses considering the impact of alternative assumptions, particularly as the proportions of individuals opting for online delivery may vary over time.

3.2.3. Outcome measures

Total discounted costs and quality adjusted life years (QALYs) for the intervention and comparator arms will be calculated over the time horizon of the analyses. An incremental cost-effectiveness analysis comparing both trial arms will be conducted. Furthermore, these results will also be presented as a return on investment, in which QALYs are valued at £20,000 per QALY (in line with NICE recommendations). Sensitivity and scenario analyses will be conducted to address key areas of uncertainty. Secondary outcome measures will include the return on investment from the perspective of clinical commissioners, 5 years, and 10 years.

We will present results comparing the reported ICERs to £20,000 per QALY gained and £30,000 per QALY gained. This is because the normal maximum acceptable ICER for a NICE appraisal committee is somewhere between £20,000 and £30,000 per QALY gained (2).

3.3. Model based economic analyses

3.3.1. Background model used

The School for Public Health Research (SPHR) type-2 diabetes treatment model, henceforth "the model", will be used to assess the cost-effectiveness of DEW versus DE. This model is an adapted version of the Diabetes Prevention model (3) used to evaluate the WRAP-UP trial. This model has been developed to evaluate the cost-effectiveness of interventions for individual with type-2 diabetes, as opposed to a population at risk of developing type-2 diabetes. This model uses the UKPDS outcomes model 2 risk equations (4) and more recently published trajectory equations for diabetes-related risk factors (5). These risk equations are more suited to a population diagnosed with type 2 diabetes, and the UKPDS data have been used in many other diabetes treatment models (6). The type-2 diabetes treatment model has been used as part of a NIHR funded programme grant to evaluate interventions to increase uptake of self-management education programmes for type 2 diabetes (7).

The model is an individual level simulation model based on the evolution of personalised trajectories for metabolic factors including body mass index (BMI), systolic blood pressure (SBP), cholesterol (LDL and HDL) and HbA1c. The model simulates the life course of an individual's characteristics and the incidence of major diabetes-related complications. All diabetes-related complications, including mortality, are estimated using the UK Prospective Diabetes Study (UKPDS) outcome model version 2 risk equations (4). In addition the model simulations other risk factors for diabetes complications as specified in the UKPDS risk equations (5). A full list of risk factors used in the UKPDS outcomes model is provided in Table 1. This table also identified which of the simulated risk factors align with the GLoW trial outcomes to enable modification of disease risk as a consequence of the intervention.

Table 1: UKPDS risk factors and comparison with GLoW trial outcomes

Risk factor	Continuous/binary	Is this outcome collected in the GLoW trial
Atrial fibrillation	Binary	No
BMI	Continuous	Yes
eGFR	Continuous	No
eGFR <60	Continuous/spline knots at 60	No
eGFR >60	Continuous	No
Haemoglobin (g/dl)	Continuous	No

HbA1c	Continuous	Yes
HDL	Continuous	Yes
Heart rate	Continuous	No
LDL	Continuous	Partial
Micro/ macroalbumuria	Binary	No
Peripheral vascular disease	Binary	No
Systolic blood pressure	Continuous	Partial
Smoker	Binary	No
White blood count	Continuous	No

The following aspects of the model will be updated:

- The patient population entering the model will be based on the individual characteristics of the participants of the GLoW trial.
- The costs of the interventions and usual care will be updated with estimates from the micro-costing and estimates from service providers.
- Changes in HbA1c and BMI for the intervention arm will be modified according to the outcomes of the GLoW trial at 12 months.
- The time taken to return to a natural history trajectory will be based on evidence from the literature.

3.3.2. Patient population

The model requires a simulated patient population with individual characteristics that impact the health trajectory in the model. We will generate a synthetic patient population by randomly sampling individual patient level data from the participants in the GLoW tria. Data for the following individual characteristics of participants collected in the trial will be used to describe their baseline characteristics: age, sex, ethnicity, duration of diabetes, smoking status, weight, height, systolic blood pressure, total cholesterol, LDL cholesterol, HDL cholesterol, and socioeconomic position. The simulated patient population will be sampled from appropriate distributions to ensure that correlation in risk factors, particularly correlation between demographic characteristics and metabolic risk factors will be preserved.

Data on risk factors that are not collected in the GLoW trial will be generated separately so that all synthetic patients have the required characteristics in the model. For variables that are not available in the trial data, we will sample values using summary data reported in economic modelling for the updated NICE National Guidelines (8). The simulated patient population will be sampled from probability distributions using this summary data and allowing for correlations between risk factors. If

no data on correlations is available, we will assume that the data not provided in the trial are independent.

3.3.3. Metabolic factors and clinical risk factors

The model will simulate metabolic risk factor trajectories for BMI, HbA1c, systolic blood pressure and HDL and LDL cholesterol. The natural history trajectories for risk factors associated with the progression of diabetes-related complications will be simulated using published equations (5). Trajectories and incidence of clinical risk factors associated with the development of micro and macrovascular diabetes complications will be simulated using UKPDS risk equations (5).

3.3.4. Treatment effectiveness after 12 months

The difference in metabolic risk factor trajectories for the DeW interventions, compared with DE will be estimated from a statistical analysis of the GLoW trial data based on the statistical analysis specified in the statistical analysis plan. This includes changes observed at 6 months and 12 months adjusting for visit, centre, randomisation characteristics, HbA1c at baseline and random intercepts for repeated observations of participant. A statistical distribution for change at 12 months will be attributed to all participants in the intervention simulation based on the mean and standard error reported. The planned analyses of the trial primary endpoint include interaction terms, including gender, socioeconomic status (Index of Multiple Deprivation), and educational attainment. If a statistically significant interaction effect is identified, these will be assessed for inclusion in the economic modelling to allow for heterogeneity in effectiveness to be described. The statistical models are designed to estimate the difference in the change in metabolic risk factors between the intervention and comparator arms at year 1.

Statistical analyses for secondary endpoints for BMI will be used to describe the difference in other metabolic risks after 12 months of follow-up. The statistical analyses will be based on estimates generated in the main statistical analysis plan, unless additional analyses planned by the health economic modelling team identify interaction effects with gender, IMD and educational status. Interaction term effects will be included in the modelling to describe heterogeneity in treatment effects if found to be statistically significant.

3.3.5. Treatment effectiveness beyond 12 months

Analysis of the WRAP 5-year follow-up identified that differences in weight loss were maintained after 5 years of follow-up but were not statistically significantly different (–0·96 (–2·90 to 0·97) kg for 12 week vs brief intervention). Therefore, in the long-term modelling it was assumed that the benefits of weight loss were diminishing linearly over time, and returned to the natural history

projection after 10 years. Differences in HbA1c were not sustained after 5 years of follow-up so the duration of benefit on HbA1c was assumed to diminish linearly over time up to 5 years after the intervention.

A systematic review and meta-analysis report pooled estimates of weight loss and HbA1c reduction for weight loss/maintenance programmes in populations with type-2 diabetes after 12 months of follow-up (9). They reported pooled estimates of differences in pooled control arms and intervention groups beyond 12 months of follow-up for weight loss. The estimates indicate that differences in the % weight loss between intervention and control are maintained after up to 4 years of follow-up. It should be noted that the uncertainty in these estimates is not reported. Pooled estimates for the difference in HbA1c beyond 12 months were not reported. One study included in this review was an intervention targeted at those with newly diagnosed diabetes (10). This was a randomised controlled trial of a Mediterranean-style diet (low carbohydrate) based in Italy. Participants in the Mediterranean diet group experienced a significant change in BMI and HbA1c at 12 months compared to the control group (low-fat diet) and these differences remained significant at 4 years.

A systematic review and meta-analysis of behaviour change techniques in diet and physical activity interventions reported difference in weight and HbA1c after 2 years of follow-up. Differences in HbA1c were statistically significant, but differences in weight were potentially clinically important, but not statistically significant (11).

The Look AHEAD trial reported the effect of a weight loss programme in individuals with type-2 diabetes on weight loss after 8 years of follow-up (12). However, the estimates from this study are considered less relevant to this analysis because the intervention included weight maintenance beyond 12 months, and included a large proportion of participants with diabetes duration more than 3 years.

Based on the available evidence it is clear that the benefits of lifestyle interventions in populations with type-2 diabetes can extend beyond 12 months of follow-up. There is evidence from a small number of studies to support an assumption that statistically significant benefits will be observed after 2 and 4 years of follow-up. It is likely that the initial differences in effectiveness will decline with time. In this modelling study we will assume that the effects of the intervention on weight loss after 12 months will decline over time, and no differences will be observed after 10 years of follow-up. Differences in HbA1c will be assumed to reduce linearly over time up to 5 years post intervention. This assumption has been used in other modelling studies (13).

3.3.6. Updated Costs and Utilities

Utility at baseline will be calculated based on an existing algorithm within the model to allow for the model to apply utility adjustment for age, gender and diabetes-related complications. Baseline EQ-5D data is available for individuals in the GLoW trial, however this data would generate inconsistencies in the model as patients develop complications. Summary data for the population will be used to benchmark baseline EQ-5D score, to which the modelling decrements will be applied.

The costs and health-state utilities relating to the complications of type-2 diabetes are based on available evidence. Table 2 describes the literature used to estimate the effects of diabetes-related complications on utilities. Diabetes related complications associated with a utility decrement will be applied multiplicatively to individual's baseline EQ-5D score. This method is preferred when individuals are at risk of developing multiple diabetes related complications. Costs of diabetes complications are taken from Alva et al. 2015 (14) and will be inflated to 2021/22 prices using price indices.

Table 2: Health-related quality of life decrements for diabetes related complications

Diabetes related complication	Mean estimate	Standard deviation	Source
Mycardial Infarction - event	0.065	0.03	Alva et al. 2014 (15)
Myocardial infarction – history	0.008	0.024	Alva et al. 2014 (15)
Stroke	0.099	0.035	Hayes et al. 2016 (16)
Ischemic Heart Disease	0.01	0.029	Hayes et al. 2016 (16)
Congestive Heart Failure	0.045	0.040	Hayes et al. 2016 (16)
Blindness	0.033	0.027	Hayes et al. 2016 (16)
Foot Ulcer	0.17	0.019	Bagust and Beale 2005 (17)
Amputation	0.172	0.045	Alva et al. 2014 (15)
MMALB	0.018	0.022	Bagust and Beale 2005 (17)
ESRD	0.049	0.068	Hayes et al. 2016 (16)
Peripheral Vascular disease	0.061	0.015	Bagust and Beale 2005 (17)

3.3.7. Weight loss and Utilities

A recent study reported a statistical association between BMI and health-related quality of life, measured using the EQ-5D-3L (18). The study reported that a unit increase in BMI would lead to an improvement in EQ-5D-3L of -0.0121 (95% CI -0.00818, -0.01602). This relationship between BMI and EQ-5D-3L will be included in the modelling to capture short-term gains to health-related quality of life. The association between weight loss and health-related quality of life will be implemented for

changes to BMI above 25kg/m^2, to be consistent with evidence from the literature. This ensures that changes to BMI within the normal range do not lead to changes in health-related quality of life.

3.3.8. Analysis

Our primary analysis will consist of a probabilistic sensitivity analysis (PSA), in which all parameters are sampled from their uncertain distributions. A set of results is produced for each run. We will calculate the mean costs and QALYs accrued across all conducted PSA runs. We will determine the number of PSA runs analytically, so this cannot be pre-specified. We will present the results of the probabilistic sensitivity analysis using a cost-effectiveness plane and Cost-Effectiveness Acceptability Curve. We explore the effect of key uncertainties in the evidence base using scenario analyses, in which certain assumptions or data are changed. Details of our pre-specified scenario analyses are provided in Section 4.

4. Pre-specified sensitivity analyses

This section of the HEDMAP details our pre-planned sensitivity analyses. We reserve the right to add additional sensitivity analyses, as key uncertainties in the evidence base are likely to become apparent during our analyses. Our pre-specified analyses are listed below:

a. The costs of DeW and DE will be varied, according to the uptake of online vs face-to-face delivery.
b. We will conduct an alternative statistical analysis of the primary endpoint in which the difference in HbA1c is estimated using a beta-regression. This regression method will generate a mean change in HbA1c and variance in change in HbA1c to allow for heterogeneity and skewness in HbA1c change to be modelled using an appropriate statistical distribution.
c. The analysis will be stratified according to baseline participant criteria including
    i. Years since diabetes diagnosis
    ii. IMD quintile
    iii. BMI categories (28-30kg/m2: 30-35kg/m2: 35-40kg/m2; 40kg/m2+)
d. We will investigate alternative assumptions about what happens to metabolic trajectories beyond 5 years in intervention arms.
    i. Change in metabolic risks return to natural history after 3 years
    ii. Change in metabolic risks return to natural history after 15 years

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