GLoW: Health Economic Analysis Plan (HEAP) for the 12-month within-trial analysis

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1. Abbreviations

BMI	Body mass index
CEAC	Cost-effectiveness acceptability curve
CHEERS	Consolidated Health Economic Evaluation Reporting Standards
CI	Confidence interval
DE	Diabetes education programme
DEW	Tailored diabetes education and behavioural weight management programme
EQ-5D-5L	EuroQoL 5 dimensions 5 level
GLoW	Glucose Lowering through Weight management
GP	General practitioner
HEAP	Health economic analysis plan
HRQL	Health related quality of life
MI	Multiple imputation
MICE	Multiple imputation by chained equations
NHS	National Health Service
NMB	Net monetary benefit
QALYs	Quality-adjusted life years
SE	Standard error
T2D	Type 2 diabetes

2. Study summary

For further details see Ahern *et al.*[1]

Aim: The Glucose Lowering through Weight management (GLoW) trial aims to evaluate whether a tailored diabetes education and behavioural weight management programme (DEW) is more effective and cost-effective than a diabetes education (DE) programme (usual care) in helping people with overweight or obesity and a recent diagnosis of type 2 diabetes (T2D) to lower their blood glucose, lose weight and improve other markers of cardiovascular risk.

Study design: Pragmatic, randomised, single-blind, parallel group, two-arm, superiority trial.

Participants: 576 adults with body mass index (BMI >25 kg/m^2 and diagnosis of T2D in the past 3 years and randomise them to a tailored DEW or a DE programme.

Primary outcome: 12-month change from baseline in glycated haemoglobin **(**HbA1c).

Secondary outcomes: the 6-month change from baseline in HbA1c; the 6-month and 12-month changes from baseline in body weight, body fat percentage, systolic and diastolic blood pressure, total cholesterol, high-density lipoprotein cholesterol and low-density lipoprotein cholesterol; good glycaemic control (HbA1c <53 mmol/mol) at 6 and 12 months; remission from diabetes (HbA1c <48 mmol/mol and without glucose-lowering medication for ≥2 months) at 6 and 12 months; weight loss ≥5% and ≥10% of initial body weight at 6 and 12 months; and, modelled cardiovascular risk (using a risk prediction model from the UK Prospective Diabetes Study, UKPDS) at 12 months.

3. Purpose of this HEAP

This HEAP describes the 12-month within-trial health economic analyses that form part of the GLoW study, referred to in the published protocol. These analyses will be pre-specified in order that they are not affected by the collected trial data after unmasking. Note there is a separate Health Economic and

[1] Ahern AL, Woolston J, Wells E, et al. Clinical and cost-effectiveness of a diabetes education and behavioural weight management programme versus a diabetes education programme in adults with a recent diagnosis of type 2 diabetes: study protocol for the Glucose Lowering through Weight management (GLoW) randomised controlled trial. *BMJ Open* 2020;10:e035020. doi:10.1136/ bmjopen-2019-035020

Decision Modelling Analysis Plan, which should be read in conjunction with the present document, and which describes a model-based economic analysis taking a lifetime time horizon.

4. Aim of this health economic analysis

The aim is to evaluate the cost-effectiveness of the DEW programme versus the DE programme from a UK NHS and social services perspective, using individual level data collected in GLoW, undertaking a 12-month within-trial analysis only.

5. Overview of health economic analysis

The analysis will be a cost-effectiveness analysis and a cost-utility analysis based on patient-level intervention costs, NHS and social services resource use, health outcomes (changes in HbA1c, changes in weight in kg), and health related quality of life (HRQL) assessed in the trial between baseline and 12 months. For the cost-effectiveness analyses we will calculate the incremental cost per unit change in HbA1c (this is the primary economic analysis) and the incremental cost per unit change in weight (secondary economic analysis). For the cost-utility analysis (also a secondary economic analyses) we will calculate the incremental cost per quality-adjusted life year (QALY) gained and the incremental net monetary benefit (NMB). The time horizon will be the within-trial period only (12 months). The perspective will be the NHS and social services. All costs will be reported in 2021/2022 UK£.

6. Identification of resources

In keeping with the study perspective the following costs will be included:

- Tailored DEW programme
- DE programme (usual care)
- In-patient hospital visits (overnight stays)
- A&E (including minor injury units and walk-in centres) visits
- Outpatient visits
- Day hospital visits
- General practitioner visits
- Nurse visits
- NHS physiotherapist visits
- NHS dietician visits
- NHS counsellor visits
- Visits to an NHS weight management service
- Visits to an education or peer support group
- Meals on wheels deliveries
- Home care attendant visits
- Prescribed medications taken for reasons relating to weight and/or diabetes

In addition the following costs, which are incurred by the individual, will be reported but not included in the cost-effectiveness analyses and cost-utility analysis given the study perspective:

- Visits to a commercial weight management group
- Visits with a private dietitian
- Visits with a personal trainer
- Visits with a private osteopath
- Visits with a private physiotherapist
- Visits with a private chiropractor
- Visits with a private chiropodist
- Visits with a private physiotherapist

- Over-the-counter (non-prescribed) products, including medications, herbal medicines, vitamins, homeopathic remedies, slimming products, or dressings/wound care items for reasons relating to weight and/or diabetes

7. Measurement of resource use

Resource use will be collected at baseline (covering the previous 3 months), at 6 months (covering the previous 6 months) and at 12 months (covering the previous 6 months) using retrospective participant questionnaires.

8. Unit costs

We will undertake a micro-costing of the DE programme to calculate the mean cost per participant. The costs of the DEW programme will be based on the commissioned costs per participant. All resource use relevant to the NHS and social services perspective will be valued using UK unit costs (in 2021/2022 £). Unit costs will be identified from published sources, such as *Unit Costs of Health and Social Care*,[2] *Prescription Cost Analysis*,[3] and *NHS Reference Costs*.[4] A table of unit costs, together with their sources will be produced and inflated to 2021/2022 prices using NHS Pay and Prices Indices[2] for each base year.

9. Total costs

The cost of all reported resource use (relevant to an NHS and social services perspective) will be calculated for each participant. These figures will then be summed for each participant, giving a total cost over the 12-month time horizon period. For both treatment arms, a mean cost per participant will be calculated.

10. Reporting of resource use and cost data

Mean (std.dev.) resource use per participant will be estimated for each item of resource use for each randomised group. Mean difference (95% CI) in mean resource use between arms will be presented. Mean (std.dev.) total cost per participant will be estimated for each randomised group. Mean difference (95% CI) in mean total costs between arms will be presented (unadjusted). These data will not be adjusted for missing data.

11. Identification of outcomes

The primary economic analysis outcome measure will be the change in HbA1c collected at baseline and 12 months. A secondary economic analysis outcome measure will be the change in weight in kg collected at baseline and 12 months. A further secondary economic outcome measure will be quality-adjusted life-years (QALYs) estimated using utility scores obtained using the EQ-5D-5L instrument[5] collected at baseline, 6 months and 12 months.

12. Measurement of QALYs

Responses to the EQ-5D-5L will be converted to utility scores using UK preference weights in line with recommendations at the time of analysis (currently the Hernandez-Alva algorithm[6]). QALYs will be calculated for each individual patient assuming a straight-line relationship between the utility score at baseline, 6 months and 12 months. QALYs will be calculated as the area under this line, computed as the ((utility score at baseline + utility score at 6 months)/4) +((utility score at 6 months + utility score at 12 months)/4). Any patient who died during the 12-month follow-up period will be assigned a utility score

[2] https://www.pssru.ac.uk/project-pages/unit-costs/
[3] https://www.nhsbsa.nhs.uk/prescription-data/dispensing-data/prescription-cost-analysis-pca-data
[4] https://www.england.nhs.uk/national-cost-collection/
[5] https://euroqol.org/eq-5d-instruments/eq-5d-5l-about/
[6] Hernández-Alava M, Pudney S. eq5dmap: A command for mapping between EQ-5D-3L and EQ-5D-5L. The Stata Journal 2018;18:395-415. https://www.stata-journal.com/article.html?article=st0528

of zero at their time of death and their QALYs will be calculated as above based on the straight-line relationship between their utility score at baseline and zero at the date of death.

13. Reporting of utility scores and QALYs

Mean (std.dev.) utility scores per participant at baseline, 6 months and 12 months will be estimated for each randomised group. Mean difference (95% CI) in mean utility scores between arms will be presented. Mean (std.dev.) QALYs per participant will be estimated for each randomised group. Mean difference (95% CI) in mean QALYs between arms will be presented (unadjusted). These data will not be adjusted for missing data.

14. Time horizon and discounting

Costs and outcomes will be valued over a 12-month time horizon. Costs and outcomes will not be discounted given that the time horizon is 12 months.

15. Missing data

We will summarise the amount of missing data for resource use and outcomes and multiple imputation (MI) will be performed (assuming missingness at random) to replace each missing observation with a set of imputed values following the method recommended by Faria et al.[7] for the imputation of economic data. We will use multiple imputation by chained equations (MICE), and Rubin's rules[8] will be implemented for the subsequent analysis of multiple datasets.

16. Measuring cost-effectiveness

Costs and outcomes will be calculated per patient and then analysed using generalised linear models controlling for covariates to estimate the incremental mean costs and outcomes of the tailored DEW programme versus the DE programme (usual care). Covariates considered will be the same as for the main statistical analysis, including centre, sex, diabetes duration and baseline value of HbA1c; we will also adjust for baseline utility score (for QALYs) and costs during the 3 month period prior to baseline (for costs).[9] ICERs and incremental NMBs will be calculated at thresholds of £13,000, £20,000 and £30,000 per QALY. The probability of the DEW programme being cost-effective compared with the DE programme at different cost-effectiveness thresholds will be calculated[10] and represented visually as a cost-effectiveness acceptability curve (CEAC).[11]

17. Reporting cost-effectiveness

Analyses will be performed on an intention-to-treat basis and following the reference case outlined in NICE guidelines.[12] Incremental costs (mean, 95% CI), incremental changes in HbA1c and weight (mean, standard errors (SEs), 95% CI), QALYs gained (mean, standard errors (SEs), 95% CI), incremental costs per QALY gained (mean, 95% CI), incremental net monetary benefits (mean, 95% CI) and the probability that the DEW programme is cost-effective at thresholds of £13,000, £20,000 and £30,000 per QALY will be reported for (1) the base case (missing values imputed using MI, with adjustment for potential confounders), (2) with missing values imputed using MI but with no adjustment for potential

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[7] Faria R, et al. A guide to handling missing data in cost-effectiveness analysis conducted within randomised controlled trials. Pharmacoeconomics. 2014;32(12):1157–70.
[8] Little RJ, Rubin DB. Statistical analysis with missing data, vol. 333. Hoboken: Wiley; 2014.
[9] Manca A, Hawkins N, Sculpher MJ. Estimating mean QALYs in trial-based cost-effectiveness analysis: the importance of controlling for baseline utility. Health Econ. 2005;14(5):487–96.
[10] Fenwick E, Claxton K, Sculpher M. Representing uncertainty: the role of cost-effectiveness acceptability curves. Health Econ. 2001;10(8):779–87.
[11] van Hout BA, et al. Costs, effects and C/E-ratios alongside a clinical trial. Health Econ. 1994;3(5):309–19.
[12] https://www.nice.org.uk/process/pmg36/resources/nice-health-technology-evaluations-the-manual-pdf-72286779244741

confounders, (3) with no MI but adjustment for potential confounders, and (4) with no MI or adjustment for potential confounders (covariates included in the main statistical analysis – see above).

We will reporting cost-effectiveness findings for subgroups of participants, using identical subgroups to those described in the statistical analysis plan (gender, index of multiple deprivation, educational qualification, and duration of diabetes).

18. Additional analyses

We have identified nine "costs" that will be reported but not included in the cost-utility analysis (section 6). By study group we will report mean values, SEs and 95% CIs for each continuous variable, and proportions for each categorical variable.

19. Sensitivity analysis

CEACs will be generated via non-parametric bootstrapping with 5,000 replications to accommodate sampling uncertainty and varying levels of the cost-effectiveness threshold for an additional unit change in HbA1c and weight and an additional QALY.

Univariate deterministic sensitivity analyses (varying one variable at a time) will examine the impact on the cost-effectiveness results of varying the intervention costs of the DEW and DE programmes, and volume and resource use and unit cost for each cost component, and utility scores. We will also calculate the unit cost of the DEW programme and HRQL gains required for the intervention to be cost-effective (for the ICER to equal the cost-effectiveness threshold).

20. Statistical packages

All analyses will be performed using Stata software.

21. Reporting

A Consolidated Health Economic Evaluation Reporting Standards (CHEERS) checklist will be reported,[13] which makes recommendations as to what ought to be reported in an economic evaluation in six main categories (title and abstract, introduction, methods, results, discussion, other), requiring a brief summary of how each aspect is reported and details of where it is reported in the text.

[13] Husereau Don, Drummond Michael, Petrou Stavros, Carswell Chris, Moher David, Greenberg Dan et al. Consolidated Health Economic Evaluation Reporting Standards (CHEERS) statement BMJ 2013; 346 :f1049