Statistical Analysis Plan

Title: Evaluating the long term impact of weight-loss programme referrals for adults in primary care on body weight and diabetes risk: 5-year follow up of the WRAP trial

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Author: Nazrul Islam

Reviewers: Amy Ahern, Simon Griffin, Stephen Sharp, Graham Wheeler, Susan Jebb, Paul Aveyard, Emma Boyland

1 Introduction

This analysis plan is for the 5-year follow up of the Weight Loss Referrals for Adults in Primary Care (WRAP) trial.[1]

The WRAP trial evaluated three weight management programmes: brief intervention, 12 week referral to a commercial programme (WW, formerly Weight Watchers), and 52-week referral to the same programme. The 52-week programme achieved greater weight loss and reductions in HbA_{1c} than 12-week programme or brief intervention over 2 years, and this effect is not moderated by sex, age or socioeconomic status. Long-term cost-effectiveness of 52-week programme depends on assumptions about weight regain.

Evaluating 5-year outcomes will enable precise measurement of the impact of the 12- and 52-week programmes on body weight, glycaemia, and incidence of type-2 diabetes, and facilitate more informed evaluation of cost-effectiveness.

This document describes the statistical analysis plan for the estimation of treatment effectiveness at 5 years. A cost-effectiveness analysis will also be performed; full details of the proposed analysis will be given in a separate document.

2 Study outcomes

2.1 Primary outcome

5-year change in weight (kg) from baseline

2.2 Secondary outcomes

Continuous outcomes

5-year change from baseline in the following—

- HbA_{1c} (%)
- HbA_{1c} (mmol/mol)
- Fat mass (kg)
- Triglycerides (mmol/L)
- Total cholesterol (mmol/L)
- LDL cholesterol (mmol/L)
- HDL cholesterol (mmol/L)
- Systolic blood pressure (mm Hg)
- Diastolic blood pressure (mm Hg)
- Modelled 10-year cardiovascular risk (%) using QRISK2 prediction model* [2]

Binary outcomes

- Transition from non-diabetic hyperglycaemia (HbA_{1c} 6.0-6.49% [42-47 mmol/mol]) at baseline to diabetes (HbA_{1c} ≥6.5% [≥48 mmol/mol]) at 5 years*.

- Transition from normoglycaemia HbA_{1c} <6.0% [<42 mmol/mol] or non-diabetic hyperglycaemia at baseline to diabetes at 5 years*.

* = outcomes not measured in the two year trial.

3 Analysis population

The analysis will be based on the intention-to-treat principle, whereby all individuals are included in the group to which they were randomised, regardless of the extent to which they adhered to the intervention.

4 Descriptive analyses

The following baseline characteristics of the study population will be summarised separately within each randomised group:

- Age (years)
- Sex
    - Female
    - Male
- Ethnicity
    - Asian or Asian British
    - Black or Black British
    - Mixed or multiple ethnic group
    - White or White British
    - Other
- Educational qualifications
    - Higher degree or equivalent
    - University degree or equivalent
    - Post-secondary education
    - A-levels or equivalent
    - GCSEs or equivalent
    - None
- Gross household income (per annum)
    - <£20,000
    - £20,000–39,999
    - ≥£40,000
- Weight (kg)
- Height (cm)
- Body-mass index (kg/m^2)
- Fat mass (kg)
- Waist circumference (cm)
- Systolic blood pressure (mm Hg)
- Diastolic blood pressure (mm Hg)

- HbA_{1c} (mmol/mol)

- HbA_{1c} (%)

- Triglycerides (mmol/L)

- Total cholesterol (mmol/L)

- LDL cholesterol (mmol/L)

- HDL cholesterol (mmol/L)

For continuous variables, means and standard deviations (SDs) will be presented, unless the variable has a skewed distribution, in which case medians, 25^{th} and 75^{th} percentiles will be presented. For categorical variables, the number and percentage of individuals within each category will be presented. For each variable (continuous or categorical), the percent of missing values will be reported. For the categorical variables, percentages within sub-categories will be calculated using the number of non-missing values as the denominator.

As recommended by CONSORT guidelines,[3] no p-values will be calculated for this table.

5 Analyses of study outcomes

5.1 Primary outcome

The mean and SD of weight at baseline and 5-year follow-up will be presented, together with the mean and SD of change from baseline, separately in each randomised group.

The primary analysis will compare 5-year change in weight from baseline between the three randomised groups, adjusting for baseline weight and research centre using ANCOVA (analysis of covariance). If there is an overall significant difference ($p<0.05$) between the three groups based on an F-test, then differences and 95% confidence intervals comparing 52-week programme vs. brief intervention, 52-week programme vs. 12-week programme, and 12-week programme vs. brief intervention group will be estimated. A secondary analysis will compare 52-week programme and the other groups (12-week programme and brief intervention) combined (if there is no significant difference between the brief intervention and 12-week programme as was the case at 2 years).[1] If measured weight is not available, we will use the most recent clinical record of measured weight, where this is no more than 12 months prior to the 5-year visit due date. Self-reported weights will be used where measured weights or clinical records are not available.

5.2 Secondary outcomes

For HbA_{1c} and other continuous outcomes, the analyses will use the same method as described in section 5.1. Variables with a skewed distribution will be log-transformed prior to analysis.

If HbA_{1c} was not measured at the study visit, we will use the most recent clinical record of HbA_{1c} where this is no more than 12 months prior to the 5-year visit due date. Proportions of incident cases of diabetes at follow-up will be presented overall, and by baseline diabetes status (normoglycaemia and non-diabetic hyperglycaemia). Incident diabetes will be defined as an HbA_{1c} ≥6.5% [≥48 mmol/mol], or a clinical diagnosis or documented history of current treatment for diabetes (in that order) (*Figure 1*) and those with diabetes at baseline will be excluded. The three randomised groups will also be compared in terms of (i) the proportion of individuals who transition

from non-diabetic hyperglycaemia at baseline to diabetes at 5 years, and (ii) the proportion of individuals who transition from normoglycaemia/non-diabetic hyperglycaemia at baseline to diabetes at 5 years. Those with a valid HbA_{1c} at baseline will be eligible for this analysis, and those with valid data on HbA_{1c} or a clinical diagnosis or diabetes medication at 5-year follow-up will be included in this analysis. Binomial regression (or logistic regression if the model does not converge) will be used for the analysis.

Statistical analyses will be conducted in Stata statistical software SE 15.1 (College Station, TX: StataCorp LLC).

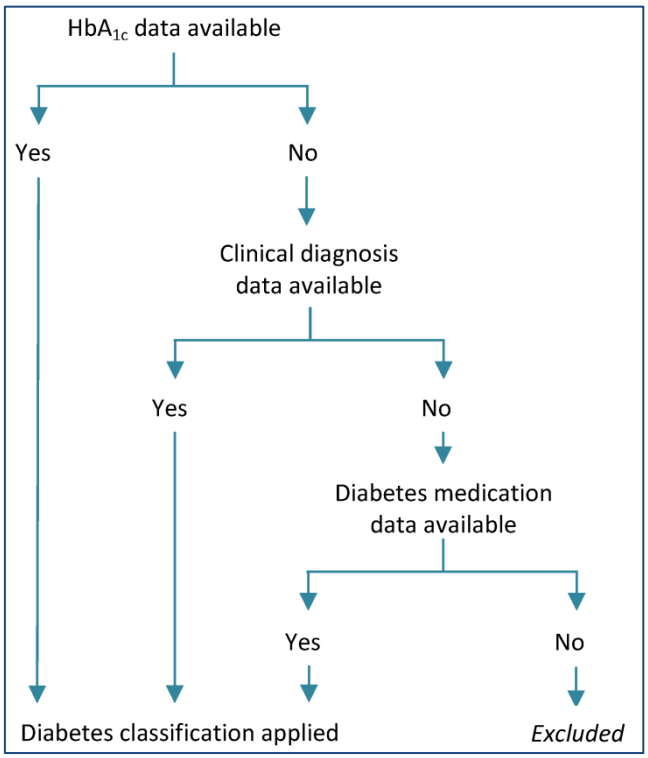

Figure 1: Proposed algorithmic presentation of diabetes status classification

6 Considerations for analysis

6.1 Missing data

Missing values of outcomes at baseline

For continuous outcomes, those participants with a missing baseline value of the variable will be included in the analysis using the missing indicator method,[4] which is a valid method for pre-randomisation measures in trials, ensuring that, other than participants with missing outcome data (see below), no further participants are excluded, thereby maximising precision of the effect size estimates.

Missing values of outcomes at 5 years

For each outcome in turn, if >10% of individuals have missing values of the outcome at 5 years, a multiple imputation model using chained equations will be used which includes values of the outcome at previous time-points as well as other baseline characteristics that have univariate associations with missingness ($p<0.2$). This model assumes that missing data are missing at random.

6.2 Subgroup analyses

For the primary outcome, potential interactions between the interventions and sex, educational qualifications (as a binary variable grouping all education categories up to and including A-levels as 'below post-secondary' and categories above A-levels as 'post-secondary and above'), and baseline diabetes status (normoglycaemia/non-diabetic hyperglycaemia vs. diabetes) will be tested by including the relevant multiplicative parameters in the ANCOVA model, e.g. 12-week programme (vs. brief intervention) x sex and 52-week programme (vs. brief intervention) x sex. If the overall F-test for interaction is statistically significant ($p<0.05$), then the intervention effects and 95% confidence intervals will be estimated within the relevant subgroups defined by the interaction variable.

6.3 Multiplicity

Due to the multiplicity of outcomes and comparisons, p-values will only be reported for the main effects and interaction analyses of the primary outcome; 95% confidence intervals will be reported all outcomes/comparisons. Results will be interpreted with appropriate caution.

6.4 Sensitivity analysis

For weight and HbA_{1c} sensitivity analysis will include (i) effects estimates adjusted for the follow-up time, and (ii) completers-only analysis. For the analyses of incident diabetes, women who are defined as a case of diabetes solely based on a history of treatment with metformin (and no other treatments) will be included as not having diabetes. This is because metformin can be prescribed for other indications, particularly in women (e.g., polycystic ovarian syndrome).

7 References

1. Ahern AL, Wheeler GM, Aveyard P, et al. Extended and standard duration weight-loss programme referrals for adults in primary care (WRAP): a randomised controlled trial. Lancet. 2017;389(10085):2214-25

2. Hippisley-Cox J, Coupland C, Vinogradova Y, et al. Predicting cardiovascular risk in England and Wales: prospective derivation and validation of QRISK2. BMJ. 2008;336(7659):1475-82

3. Moher D, Hopewell S, Schulz KF, et al. CONSORT 2010 statement: updated guidelines for reporting parallel group randomised trials. BMJ. 2010;340:c332

4. White IR, Thompson SG. Adjusting for partially missing baseline measurements in randomised trials. Stat Med. 2005;24:993-1007

Statistical Analysis Plan - ADDENDUM

Title: Evaluating the long term impact of weight-loss programme referrals for adults in primary care on body weight and diabetes risk: 5-year follow up of the WRAP trial.

ISRCTN64986150

Date of original SAP: 10 September 2019

Date of SAP addendum: 11 October 2021

The following post-hoc amendments were made to the SAP. Justification for these amendments is given here.

Section 5.1 – Primary outcome

The ANCOVA used for the primary analysis (and by implication all continuous secondary outcomes) will also be adjusted for gender, as well as baseline value of the outcome and research centre, as described in the original SAP. This is because gender, along with research centre, was a stratifier for the randomisation, and is consistent with the EMA Guideline on adjustment for baseline covariates in clinical trials (2015 EMA/CHMP/295050/2013), which states "*stratification variables, if not solely used for administrative reasons, should usually be included as covariates or stratification variables in the primary analysis regardless of their prognostic value.*"

Section 5.1 – Primary outcome

The requirement for an overall significant difference ($p<0.05$) between the groups based on an F-test as a pre-requisite to estimating the pairwise differences specified in the SAP has been removed. This is because the pairwise differences and their confidence intervals contain more information about the effect of each intervention than a single p-value from an F-test. It is also consistent with CONSORT recommendations for the reporting of multi-arm parallel group randomised trials (JAMA. 2019;321(16):1610-1620), which states "*One strategy is to first perform a global statistical test across all groups, and only to proceed to paired comparisons if the global test is statistically significant. This strategy does not seem especially desirable for the analysis of clinical trials, which require a more focused approach to the evaluation of treatment comparisons.*"

Section 5.2 – Secondary outcome

An additional binary secondary outcome was defined: 5-year weight at least 5% below baseline weight? (yes/no). This was included to support comparison with other similar studies where it is a commonly used outcome.

Amy Ahern, 11 October 2021