ten top tips

weight loss tips based on scientific evidence

Statistical Analysis Plan

Final Version

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Contents

Study Summary

TITLE	Randomised controlled trial of habit-based advice for weight control in general practice (10TT Trial)
DESIGN	The trial will be a two-arm, individually-randomised, controlled trial in obese adults in primary care, comparing the 10TT intervention offered in addition to 'usual care' with usual care alone.
AIMS	To test the hypothesis that a simple weight control intervention based on habit-formation theory will achieve clinically significant loss in weight over 3 months in obese primary care patients, compared with patients placed receiving 'usual care'.
OUTCOME MEASURES	Change in body weight, body mass index, waist circumference, and percentage of patients achieving 5% weight loss.
POPULATION	Obese adults in primary care.
ELIGIBILITY	Adults (age> 18) and BMI > 30.
TRIAL REGISTRATION	ISRCTN16347068

Analysis plan in protocol

(Beeken et al. 2012)

Baseline characteristics will be reported by each arm using descriptive statistics. A random effects linear regression model accounting for clustering by health professionals delivering the intervention in the intervention arm will be used to compare the weight change at 3 months from baseline between the two groups. This analysis will be adjusted for baseline weight which should make the statistical analysis more efficient. Bias due to missing data will be investigated. If required, sensitivity of the results to missing data will be investigated using different approaches for handling missing data, including adjusting for predictors of missingness that are related to the outcome, multiple imputation and baseline observation carried forward. The possibility that data may not be missing not at random (MNAR) will also be considered and if necessary approaches that can handle MNAR data will be used as part of the sensitivity analysis [28]. Additionally, the scope of incorporating information on reasons for drop-out in the analyses will also be explored.

Secondary outcomes will be compared between the intervention groups using appropriate regression models taking account of clustering. Subgroup analyses will investigate intervention effects by gender, age (in tertiles), baseline BMI (<35 vs. ≥35), ethnic origin (white vs. other) and deprivation (tertiles of postcode-based Index of Multiple Deprivation) as part of secondary analyses.

Results from all secondary analyses will be considered as exploratory.

The primary aim of the trial is to evaluate the effectiveness of offering the intervention; therefore all analyses will be performed on an intention to treat basis. A detailed analysis plan will be prepared nearer the data analysis stage.

Note: minor differences between the protocol and the final analysis plan are reported in the "Differences with original protocol" paragraph

Introduction

Purpose and scope of the Statistical Analysis Plan (SAP)

This document reports the details of the main analysis of the Ten Top Tips (10TT) trial. The aim is to pre-specify the analyses so that they are not influenced by the results after unblinding of the data. This SAP does not prevent further analyses being performed, which may become relevant while analysing the data, but they will have to be interpreted with more caution in view of the ad-hoc nature of the specification. It also does not prevent the analysis being adapted if specific situations arise during analysis, but this will have to be justified and transparent.
The SAP covers the main analyses of the trial (primary and secondary outcomes at 3 months), but not the longer term analysis (effect maintenance), nor the economic evaluation.

Writing of the SAP

This SAP was written by Rumana Omar and Baptiste Leurent, in collaboration with Jane Wardle, Rebecca Beeken, Victoria Vickerstaff and Irwin Nazareth.

This SAP was developed with access to the baseline and follow-up data collected at the time of writing, but without access to the randomisation arm, or any data that could jeopardise the blinding (eg. adherence to tips, reasons for drop out, etc…).

The final version of the analysis plan was approved by RO, BL, JW and IN.

Analysis organisation

Unblinding of the data and analysis will be initiated after the last patient has completed follow-up, all relevant data has been entered, data checking performed and the analysis plan has been finalised and approved.
Analysis programs will be prepared as much as possible before unblinding, including at least the primary analysis.
The primary analysis will be performed by two statisticians separately to insure its accuracy.

Data checking

Before analysis, basics check for abnormal data will be performed. These include:

- Missing data
- Data outside expected range
- Whether participants have answered non-applicable questions
- Other inconsistencies between variables

When inconsistencies are found, data will be double checked with the researchers and corrected if necessary, or may be set as missing otherwise. All changes will be documented.

Data collected

Baseline

- Socio-demographics (gender, age, ethnicity, qualifications, postcode)
- Anthropometrics (weight, height, waist circumference)
- Clinical (systolic and diastolic blood pressure, total blood cholesterol, LDL cholesterol and glucose levels)
- Questionnaire-based measures (see below)

3 months

- Anthropometrics (weight, height, waist circumference)
- Clinical (systolic and diastolic blood pressure, total blood cholesterol, LDL cholesterol and glucose levels).
- Questionnaire-based measures (see below)

6, 12, 18 and 24 months:

- Anthropometrics (weight, height, waist circumference)
- Questionnaire-based measures (see below)

Questionnaires-based measures:

- Diet
- Alcohol consumption
- Physical activity
- Self-efficacy confidence
- Food restraint
- Self-regulation of eating
- Social support for physical activity and healthy eating
- Health-related quality of life
- Automaticity of target behaviors

Other data available:

- Identifier of general practice
- Identifier of practice nurse providing leaflet and information (Intervention arm only)
- Index of Multiple Deprivation
- Type of ‘usual care’ offered

- Economic data (use of primary and secondary care services)
- Reasons for missing follow-up assessment (withdrawal, cannot contact, personal reason, etc.)
- Records of acute illness history (including diabetics).
- Assessment dates

Schedule summary:

Measure	**Visit**					
	Baseline	3M	6M*	12M*	18M*	24M*
Socio-demographics	X					
Anthropometrics	X	X	X	X	X	X
Clinical	X	X				
Questionnaire-based	X	X	X	X	X	X

*Note: the scope of this analysis plan is only the analysis of the baseline and 3-months data (primary outcome).

Analysis

Participants' recruitment and retention

A flow chart reporting the number of patients at each stage of the study will be reported, it will include details of number pre-recruitment (number of potentially eligible patients, number of letter sent, number of replies) and post-recruitment (randomised, completed follow-up, reason for non-completion).

Baseline description

A table will present the baseline characteristics of the participants, separated by arm. Mean (standard deviation), Median (Inter-Quartile Range) or Frequency (%) will be reported, as appropriate.

Attrition

We will use descriptive comparisons and Chi-squared tests where possible to see if the attrition rate, or reason for dropping out, differs by arm.
We will use logistic regression to compare baseline characteristics of participants who completed the 6 months visit versus those who did not. We will report the main predictors of drop out.
We will also investigate if the effect of these predictors differs by arm, testing for the presence of a treatment interaction.

Primary analysis

The primary outcome of the trial is the change in weight between baseline and 3 months.
The difference in weight change between arms will be estimated, adjusting for baseline weight (ANCOVA). To take into account of the possible variations (clustering) by health professional delivering the 10 Top Tips intervention, we will add a random effect by health professional in the intervention group, and residuals will be

allowed to vary by trial arm (ref. Roberts et al. 2005 and Walwyn et al. 2010). The model will also be adjusted for the randomisation stratification variable (general practice) to increase efficiency and correct standard errors (ref. Kahan et al. 2012).We will therefore fit the following mixed-effect (hierarchical) model:

$$Y_i = \mu + \beta_1 X_i + \beta_T T_i + u_{prac(i)} + u_{hp(i)} T_i + \varepsilon_i (1 - T_i) + \xi_i T_i$$

Where:

- Y is the outcome (change in weight)
- X is the adjustment variable (baseline weight)
- T is an dummy variable for the intervention arm (=0,1)
- β_T is the parameter of interest, adjusted difference between trial arms.
- i is the participant subscript
- $prac(i)$ is the subscript for the general practice of the participant
- $hp(i)$ is the subscript for the health professional delivering the intervention to participant i
- $u_{prac(i)}$ is a random effect at the practice level
- $u_{hp(i)}$ is a random effect at the health professional level
- $\varepsilon_i^{(1)}$ and $\xi_i^{(1)}$ are residuals at the patient level

This corresponds to the heteroscedastic model for a partially nested design suggested in Roberts et al. 2005 and Walwyn et al. 2010.

A model which assumes homogeneity of residuals between trial arm will also be fitted. If the results from this simpler model differ only a little from the heterogeneous model, then this will be considered as the final model. Initially a random effects model will be used to account for practice. However, if this model does not converge then practice will be included as fixed effects in the model.
The primary analysis will be performed on observed outcome values (without imputation).

Model checking

The validity of the primary analysis model will be evaluated by checking the normality and homoscedasticity of the residuals. The presence of highly influential

observations will also be assessed. Sensitivity analyses will be performed if necessary.

Sensitivity to clustering

We will fit a simple model using ANCOVA, adjusting for baseline weight and practice as fixed effects.

Missing covariates

Missing baseline covariates will be imputed by regression imputation, using other baseline variables as predictors. This does not bias the outcome comparison between arms, and is more efficient than excluding observations with missing covariates (ref. White et al. 2005).
Baseline description will be based on observed data and the number of missing observations will be reported.

Sensitivity to missing outcome data

We expect around 30% of randomised participants not to complete the 3-months follow-up. We will perform sensitivity analysis under various assumptions for missing outcomes.

We will perform a “Baseline Observation Carried Forward” analysis (replacing missing weight at 3 months by baseline weight).
In another sensitivity analysis, we will fit the primary analysis model, adding the main predictors of missingness as covariates.
We will also perform a multiple imputation approach. The imputation model will include the outcome of interest (weight change), socio-demographics and anthropometrics data at baseline, and any other variables possibly related to missingness and weight change. The imputations will be performed by study arm. Regarding the number of imputations, it is is sometime recommended to be around

the proportion of missingness (e.g. 30 imputed sets of data for 30% missingness). We may adapt this in consideration of the Monte Carlo error and computation time. In a further exploratory analysis, we will also include the 6-months weight in the multiple imputation model. This will allow using more information for participants who missed the 3-months assessment but for whom the weight information is available at a later date.

Both approaches above assume that the outcome is "Missing At Random" (conditionally on the covariates or imputation model, the chance of being unobserved is independent of the outcome). We will conduct further sensitivity analyses considering Missing Not At Random mechanisms. Methods to incorporate a possible "not at random" element for the missing data have been discussed (ref. Carpenter et al. 2008, Chapter 6). A pattern-mixture approach introduces an additional parameter δ to represent the mean difference in outcome for the non-respondents vs. the respondents ($(\mathrm{Y} \mid \text{covariates}, \mathrm{Y} \text{ is unobserved}) \sim (\mathrm{Y} \mid \text{covariates}, \mathrm{Y} \text{ is observed}) + \delta$).
The implementation of this approach in Stata proposed by White (ref. White 2011), appears suitable for this trial. An alternative could be the implementation of the pattern-mixture approach with multiple imputation, which has also been suggested (Carpenter et al. 2008, section 6.5).
After discussion with the principal investigator, we agreed that a "best-guess" delta would be of around +0.5 standard deviation of the observed change in weight. A range of δ from 0.0 to 1.0 standard deviation, allowed to differ by trial arm, should be sufficient to cover all plausible MNAR scenarios.

Secondary outcomes

The following secondary outcomes will also be compared between arms:
Morphologic:

- 5% reduction in weight
- Change in Body Mass Index
- Change in waist circumference

Clinical:

- Change in systolic blood pressure
- Change in diastolic blood pressure
- Change in total blood cholesterol

- Change in LDL cholesterol
- Change in glucose level

Logistic or linear regression will be used to estimate the difference between arms, adjusted for baseline weight and baseline value of the outcome. As for the primary analysis, a mixed-effect model considering practice effect and health professional clustering in the intervention group will be used if appropriate.

Sensitivity analyses will be performed as required. For example glucose level may be compared separately in diabetics and non-diabetic patients. We will also explore if adjustment for predictors of missingness, or multiple imputations of the missing data, affects findings.
For the secondary outcomes, the results will be presented as estimates with 95% CIs. P-values will not be reported. .

Subgroup analysis

In order to explore heterogeneity of the intervention effect, we will test for the presence of a difference in treatment effect (interaction) in the following subgroups:

- gender
- age (tertiles)
- baseline BMI (<35 vs. ≥35)
- deprivation (sample tertiles of postcode-based Index of Multiple Deprivation)

We will also test for a linear interaction (with the “subgroup” variable as continuous) for age, baseline BMI, and deprivation (using centiles of overall UK IMD ranks). Intervention effect estimates by subgroups will be represented in a forest-type plot. The results from these analyses will be treated as exploratory and the statistical significance of the interactions will be interpreted with caution in view of:

i) The trial is not specifically powered to test for interactions (i.e. non-significant p-values will not demonstrate absence of interaction)

ii) The exploratory nature of the subgroups and the multiple testing (i.e. p-values of borderline significance will not demonstrate presence of interaction).

Other analyses

If some baseline characteristics related to outcome seem to differ between the trial arms, an exploratory analysis adjusting for these factors will be performed.

Other outcomes, such as diet, or physical activity, have also been measured. They will be compared between trial arms in further analyses but are not included in this SAP.

As part of secondary analyses, we also intend to look if scores on the different questionnaire measured at baseline may be related to difference in intervention effects, and to explore the mediators of change in weight over time.

General statistical considerations

All analyses will be according to randomisation arm, independently of whether they received the allocated intervention (intention-to-treat).

All statistical test and confidence intervals will be 2-sided.
Significance will be considered at the 0.05 level and confidence intervals will be at the 95% level.

Statistical analysis will be performed using STATA software (version 12 or above).

Reporting

The CONSORT statement (Schulz et al. 2010) will provide guidelines for reporting. Exact reporting will depends of publications requirements.

Differences with original protocol

Adjustment for general practice in the primary model was not specifically mentioned. It is however appropriate to do so as the randomisation was stratified by practice.

It will not be possible to perform a meaningful test for a subgroups difference in intervention effect by ethnicity, as non-white represents a too small category.

Variables technical definition

(Note: `This font` indicates Stata syntax).

A window of +/- 6 weeks will be allowed for observations of the 3-months outcomes. Any assessment done less than 49 days or more than 133 days after baseline date will be excluded from the primary analysis.

Weight at 3 months= weight measured at 3 months assessment. Self-reported weight (over the phone when could not attend appointment) are not included in the primary analysis.
Weight change= weight at 3 months visit – weight at baseline visit.

Outcome change= outcome at 3-months visit – outcome at baseline.
(only complete records for reporting, using baseline-imputed values for analysis)

Age = at baseline : `round((date_0-dob)/365.25,0.01).`

5% reduction in weight:

```
gen pch=(weight_1-weight_0)/weight_0
replace pred5=1 if pch<=-0.05
replace pred5=0 if pch>-0.05 & pch!=.
```

Body mass-index:

As reported, excluding when calculated from self-reported weight.

Deprivation:

Index of multiple deprivation, obtained via UK data Service website (http://ukdataservice.ac.uk/). Based on the National Statistics Postcode Directory 2010, Indices of Deprivation 2007 LSOA ranks. Each participant's postcode was matched to the corresponding LSOA (Lower layer Super Output Area) and IMD rank. Ranks were converted into centiles.

Age subgroup by tertiles:

```
gen agecat3=(age>=0)+(age>=50)+(age>=65) if age<.
```

Deprivation subgroup by tertiles:

```
gen imdcat=(imdcent>=1)+(imdcent>=46)+(imdcent>=74) if imdcent<.
```

References

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Roberts C, Roberts SA. “Design and analysis of clinical trials with clustering effects due to treatment”, Clinical Trials 2005; 2(2):152–62.

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