Statistical Analysis Plan

Anglo-Danish-Dutch study of Intensive Treatment of people with Newly diagnosed diabetes in primary care (ADDITION): ten-year follow-up.

FINAL – 13 June 2016

INTRODUCTION

This is the plan for analyses of 10-year follow-up data from the ADDITION study.

The analyses are described in 3 sections. Section 1 describes the highest priority analyses, results from which will be presented at EASD in September 2016. The intention is to complete the analyses described in Section 2 at the same time, assuming data are available in sufficient time. The analyses described in Section 3 are more open-ended and exploratory, and will depend on the extent of missing data; these will be performed after EASD, once all available data have been received, and prior to any manuscript being submitted.

All analyses described are based on the Intention to Treat principle, i.e. participants are analysed in the group to which they were randomised.

Other analyses of 10-year follow-up data are not part of this Analysis Plan.

The analyses described in this document are compatible with the recommendations of the CONSORT 2010 statement (www.consort-statement.org).

SECTION 1

1.1 Baseline characteristics

The baseline characteristics listed below will be summarised by randomised group for the overall trial population (not by centre). This table will include more people than presented at 5 years because of further recruitment to the study in Leicester since then.

Continuous variables:

- Age.
- BMI.
- Weight.
- Waist circumference.
- HbA_{1c}
- Systolic blood pressure.
- Diastolic blood pressure.
- Total cholesterol.
- HDL cholesterol.
- LDL cholesterol.
- Triglycerides.
- Creatinine.
- Units of alcohol per week.

Binary variables:

- Sex.
- White ethnic origin.
- Employed.
- History of MI.
- History of stroke.

- Current smoker.
- Any glucose-lowering drug.
  - Metformin.
  - Sulphonylurea.
  - Thiazolidinedione.
  - Insulin.
  - Other.
- Any antihypertensive drug.
  - ACE inhibitor or ARB.
  - β-blocker.
  - Calcium-channel blocker.
  - Diuretic.
  - Other.
- Any cholesterol-lowering drug.
  - Statin.
  - Fibrate
- Aspirin.

For continuous variables, the mean and standard deviation (SD) will be presented, unless the variable has a skewed distribution, in which case the median and interquartile range (IQR) will be presented. For binary variables, the number and percentage of participants with and without the characteristic of interest will be presented.

1.2 Primary outcome

The primary outcome is "Composite CVD events", defined as development of any of the following:

- CVD mortality.
- CVD morbidity (non-fatal stroke, non-fatal MI).
- Revascularisation.
- Amputation (excludes traumatic).

The number and percentage of participants who experience this outcome will be presented by randomised group. The cumulative incidence of the outcome over time will be calculated within each randomised group using the method for competing risks (in which death from non-CV causes is the competing event) described by Gooley 1999 (implemented by the –stcompet- command in Stata), and presented graphically, as in Figure 2A of Griffin et al (2011).

A Cox regression model, with time since randomisation as the underlying timescale, will be used to estimate the hazard ratio and 95% confidence interval for the comparison of the Intensive Treatment (IT) group with the Routine Care (RC) group, separately within each centre (Cambridge, Denmark, Leicester, Netherlands). Robust standard errors which allow for intracluster correlation, where the clusters are general practices, will be calculated using the cluster() option within Stata.

The estimated hazard ratios from the 4 centres will be combined using fixed effects meta-analysis (i.e. with a fixed centre effect and common intervention effect), and a forest plot used to display the estimated effect sizes and confidence intervals for each centre and overall. A p-value for the test of the null hypothesis that there is no effect of the intervention will be calculated, as will the I^2 statistic,

representing the proportion of variability (in estimated log hazard ratios) between centres which is due to heterogeneity.

If the numbers of individuals with the primary outcome in the Leicester and Cambridge centres are insufficient to allow estimation of hazard ratios separately in these centres, the analysis of the primary outcome will be performed by country instead.

1.3 Components of the primary outcome

Each of the 4 components of the primary outcome will be analysed by country (since there will be insufficient numbers of events to analyse by centre) using Cox regression and then combined across countries using fixed effects meta-analysis as described in Section 1.2, although p-values for each component will not be calculated. Results will be presented using a forest plot as in Figure 2B of Griffin et al (2011).

1.4 All-cause mortality

All-cause mortality will be analysed by centre using Cox regression and then combined across centres using fixed effects meta-analysis as described above, although a p-value will not be calculated. Kaplan-Meier estimates of cumulative incidence over time will be calculated. Results will be presented as in Figure 3 of Griffin et al (2011).

If the numbers of deaths in the Leicester and Cambridge centres are insufficient to allow estimation of hazard ratios separately in these centres, the analysis will be performed by country instead.

1.5 Interactions/subgroup analyses

For the primary outcome, interactions between randomised group and (1) age (<60, ≥60), and (2) previous MI/stroke will be tested. The relevant interaction term will be included in a Cox model fit separately within each centre (or country, as per the analysis in section 1.2), and then the interaction parameter estimates will be combined across centres (or countries) using fixed effects meta-analysis. Hazard ratios (IT vs RC) and 95% CIs will be calculated within each of the subgroups, using the same method described in Section 1.2.

SECTION 2

2.1 Secondary continuous outcomes

- BMI.
- Weight.
- HbA_{1c}.
- Systolic blood pressure.
- Diastolic blood pressure.
- Total cholesterol.
- HDL cholesterol.
- LDL cholesterol.
- Triglycerides.

- Creatinine.
- Units of alcohol per week.

The continuous outcomes listed above will be summarised by randomised group for the overall trial population (not by centre) at baseline and 10 years using means and SDs, or medians and IQRs if the variable has a skewed distribution. The mean and SD of change from baseline to 10 years will also be calculated.

An estimate of the intervention effect (IT vs RC) on each outcome will be estimated by fitting the following linear regression model to the data from each centre separately:

Outcome at 10 years = outcome at baseline + randomised group + error

This is Analysis of Covariance (ANCOVA). Robust standard errors which allow for intracluster correlation, where the clusters are general practices, will be calculated using the cluster() option within Stata. If the variable has a skewed distribution, it will be log transformed before fitting the regression model.

The estimated intervention effect (difference IT vs RC in mean change from baseline) from each centre will be combined across centres using fixed effects meta-analysis (i.e. with a fixed centre effect and common intervention effect).

2.2 Secondary binary outcomes

- Current smoker.
- Any glucose-lowering drug.
- Any antihypertensive drug.
- Any cholesterol-lowering drug.

The binary outcomes listed above will be summarised by randomised group for the overall trial population (not by centre) at baseline and 10 years using frequencies and percentages. The change in percentage of participants with the outcome from baseline to 10 years will also be calculated.

An estimate of the intervention effect (IT vs RC) on each outcome will be estimated by fitting the following logistic regression model to the data from each centre separately:

log odds of outcome at 10 years = outcome at baseline + randomised group

Robust standard errors which allow for intracluster correlation, where the clusters are general practices, will be calculated using the cluster() option within Stata.

The estimated intervention effect (log odds ratio IT vs RC) from each centre will be combined across centres using fixed effects meta-analysis (i.e. with a fixed centre effect and common intervention effect).

2.3 Missing data

For the primary outcome, participants who are lost to follow-up will be censored at their last available follow-up time. The analysis assumes that censoring is non-informative, i.e. that the probability of experiencing an event is not affected by censoring, conditional on randomised group.

For continuous outcomes, participants with a missing baseline value of the variable, but with a value at 10 years, will be included in the analysis using the missing indicator method, which is a valid method for pre-randomisation measures in trials (White 2005) ensuring that no further participants are excluded while maintaining the advantage of improved precision.

For continuous and binary outcomes, participants with missing data at 10 years follow-up will be excluded from the analysis. This "complete-case analysis" is valid under the assumption that the outcome is missing at random (MAR), conditional on randomised group and baseline value.

SECTION 3

3.1 Impact of deviations from non-informative censoring on analysis of primary outcome

Analysis of the primary outcome assumes non-informative censoring. A sensitivity analysis will be performed using the approach described by Jackson (2014) and implemented in R (R Core Team 2015). In this approach, multiple imputation is used to impute censored event times, making different assumptions about how the hazard of an event changes at censoring, and using bootstrapping to take into account the uncertainty in the imputation model.

3.2 Summary of missing data for secondary outcomes

The number and percentage of missing values at 10 years of the variables listed below (which are considered the most important of the secondary outcomes) will be reported by centre:

- Weight.
- HbA_{1c}.
- Systolic blood pressure.
- Diastolic blood pressure.
- Total cholesterol.

For each of these variables, if more than 10% of values at 10 years are missing, the baseline characteristics listed below will be summarised with participants categorised by whether or not their value at 10 years is missing. Univariate logistic regression, with robust standard errors to allow for clustering by general practice, will be used to test whether each characteristic is associated with the probability of missingness.

- Age.
- BMI.
- Weight.
- Waist circumference.

- HbA_{1c}.
- Systolic blood pressure.
- Diastolic blood pressure.
- Total cholesterol.
- HDL cholesterol.
- LDL cholesterol.
- Triglycerides.
- Creatinine.
- Units of alcohol per week.
- Sex.
- White ethnic origin.
- Employed.
- History of MI.
- History of stroke.
- Current smoker.
- Any glucose-lowering drug.
- Any hypertensive drug.
- Any cholesterol-lowering drug.

3.3 Sensitivity analyses

The analysis of secondary outcomes described in Section 2 assumes missing data at 10 years are missing at random (MAR), conditional on randomised group and baseline value. If any of the 5 secondary outcome variables listed in Section 3.2 are missing in more than 10% of participants at 10 years, 2 exploratory sensitivity analyses will be performed, investigating different assumptions about the missing data:

1. MAR, conditional on additional baseline characteristics.

The same ANCOVA approach described in Section 2, but also including any baseline characteristics which are associated with missingness identified in Section 3.2, will be applied.

2. Impact of plausible departures from MAR on the estimated intervention effect.

To investigate the potential impact of plausible departures from MAR on the estimated intervention effect, the approach described by White et al (2012) will be used, which is based on jointly modelling the data and the missingness using a pattern mixture model. A parameter δ is defined which represents the difference between the mean of the observed outcome and the mean of the unobserved values. Under the MAR assumption, $\delta=0$. The impact on the intervention effect of varying δ in one or both of the treatment groups will be displayed graphically.

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