

Statistical Analysis Plan

ADDITION

1. Introduction

The ADDITION (Anglo-Danish-Dutch study of Intensive Treatment in people with screen detected diabetes in primary care) trial was set up in three countries – Denmark, England (Cambridge and Leicester) and the Netherlands, to provide evidence on screening for type 2 diabetes and the effects of intensive multifactorial treatment among screen-detected patients.

This is the plan for the analyses of the primary, secondary and intermediate endpoints from the ADDITION trial, including all five year follow-up data from Cambridge, Leicester, Denmark and the Netherlands.

A separate plan, following similar principles, will be prepared for the analysis of secondary microvascular endpoints. Further analysis plans will also be developed for the assessment of the cost-effectiveness of the intervention, patient satisfaction with the intervention, and the impact of the intervention on quality of life. Subsequent cohort and process analyses will also be performed; details of these analyses are not described here, although some of the analysis principles may still apply.

2 Study endpoints

2.1 Primary endpoint

The primary endpoint will be composite cardiovascular events, a binary variable indicating whether or not each participant experienced any of the following events as verified by the trial endpoints committee: cardiovascular mortality, cardiovascular morbidity (i.e. non-fatal myocardial infarction, non-fatal stroke), revascularisation, amputation. Time to event analysis will be used as described in section 5.

2.2 Secondary endpoints

Each of the individual components of the primary endpoint along with all-cause mortality will be analysed as a separate, secondary endpoint. Time to event analysis will be used as described in section 5.

2.3 Intermediate endpoints

Intermediate endpoints which will be assessed are as follows:

- HbA1c (%).
- Total cholesterol (mmol/l).
- LDL cholesterol (mmol/l).
- HDL cholesterol (mmol/l).
- Triglycerides (mmol/l).
- Systolic blood pressure (mmHg).

- Diastolic blood pressure (mmHg).
- Modelled ten year cardiovascular risk, using the UKPDS CVD risk score (%).
- New prescriptions during follow-up (either self-reported at 5 years or recorded on the GP database at 5 years) of the following:
 - hypoglycaemic medications.
 - antihypertensive medications.
 - ACE inhibitor/angiotensin receptor blockers.
 - statins.

3 Analysis population

The primary trial analysis will use an **Intention To Treat (ITT) population**, which includes all participants in the group to which they were randomised, regardless of the amount of intervention actually received. Those participants with missing data for an outcome will be excluded from the primary analysis of that outcome (see section 6.2).

A Per-Protocol population will also be defined, based on adherence to study treatment guidelines in the intervention group. This will be defined prior to assessment of differences in outcomes between per protocol sub-groups by study group.

4 Descriptive analyses

The following descriptive tables will be presented, by randomised group, overall, and separately for each centre:

- Baseline characteristics of general practices.
- Baseline characteristics of individuals.

For continuous variables, means and standard deviations will be presented, unless the variable has a highly skewed distribution, in which case, medians, 25th and 75th 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 % of missing values will be reported.

No p-values will be calculated for these tables.

5 Analyses of study endpoints

5.1 Primary and secondary endpoints

For each of the endpoints defined in Sections 2.1 and 2.2, the number and percentage of individuals experiencing the endpoint will be presented, by randomised group, along with the median and interquartile range of the time to event/censoring. Plots of the cumulative incidence of each endpoint, by randomised group, will be calculated using the method

described by Gooley 1999 (and implemented by the `-stcompet-` command in Stata), and presented graphically.

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 intervention group with the routine care group separately within each centre. The standard errors will be adjusted to allow for intracluster correlation, where the clusters are the general practices, using the `cluster()` option within Stata.

The estimated hazard ratios from the four centres will then be pooled 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. The I^2 statistic, representing the proportion of variability (in estimated log hazard ratios) between centres which is due to heterogeneity, will be calculated.

For the primary endpoint, the intracluster correlation coefficient (i.e. the proportion of the total variance in the probability of the primary endpoint that is due to variation between general practices) will also be reported, separately within each country and overall.

The assumption of proportional hazards will be tested by including a parameter for treatment x time interaction in each of the centre-specific Cox regression models; the centre-specific parameter estimates will then be pooled using fixed effects meta-analysis. If the pooled estimate is significantly different from 0, this will provide evidence against the proportional hazards assumption. This approach is described in the paper "Statistical methods for the analysis of individual participant data from multiple epidemiological studies" (Emerging Risk Factors Collaboration, IJE to appear 2010).

5.2 Continuous intermediate endpoints

For each of the continuous intermediate endpoints defined in section 2.3, a normal errors regression model will be used to estimate the difference in mean change from baseline, and 95% confidence interval, comparing the intervention group with the routine care group. The baseline measure of the outcome will be included as a covariate in the model. The standard errors will be adjusted to allow for intracluster correlation, where the clusters are the general practices, using the `cluster()` option within Stata. If the distribution of the outcome is skewed, a log transformation will be used.

The estimated differences in means from the four centres will then be pooled 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. The I^2 statistic, representing the proportion of variability (in estimated differences in means) between centres which is due to heterogeneity, will be calculated.

As well as presenting the estimated differences between the intervention and the routine care groups, the mean change from baseline to follow-up within each group will be estimated, together with a 95% confidence interval. These mean changes will be calculated using data from all four centres combined.

5.3 Binary intermediate endpoints

Each of the binary intermediate endpoints defined in section 2.3, i.e. the prescription endpoints, will be summarised by presenting the number and percentage of individuals prescribed each class of drugs within the intervention group and routine care group, by centre and overall.

A logistic regression model will be used to estimate the odds ratio and 95% confidence interval for the comparison of the intervention group with the routine care group separately within each centre. The standard errors will be adjusted to allow for intracluster correlation, where the clusters are the general practices, using the `cluster()` option within Stata.

The estimated odds ratios from the four centres will then be pooled 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. The I^2 statistic, representing the proportion of variability (in estimated log odds ratios) between centres which is due to heterogeneity, will be calculated.

6 Considerations for analysis

6.1 Minimisation stratifiers

The minimisation stratifiers that were incorporated into the practice randomisation differed by centre. In the 1 year analysis of ADDITION-Cambridge, the effect of the intervention remained similar after adjustment for these stratifiers. Therefore for the five year analysis of the combined data from all four centres, no adjustment will be made for the minimisation stratifiers. A sensitivity analysis comparing centre-specific intervention effects adjusted and unadjusted for centre-specific minimisation stratifiers will be performed for the primary outcome.

6.2 Missing data

The primary trial analysis will use an Intention To Treat (ITT) population, which includes all participants in the group to which they were randomised, regardless of the amount of intervention actually received. For the primary and secondary endpoints, individuals who were lost to follow-up will be considered as censored. For the intermediate continuous endpoints, individuals who were lost to follow-up, or who died during the 5 year follow-up period, will be excluded. We will describe the pattern of missing data.

Missing baseline values of outcomes

For continuous outcomes, those participants with a missing baseline value of the variable 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.

6.3 Source of measurement for intermediate outcomes

Because some of the anthropometric measures and blood test results were performed in the general practices, sensitivity analyses will be performed to assess whether there are any differences between the results using the centrally measured values and the locally measured values of these outcomes.

6.4 Subgroup analyses

For the primary endpoint, the Cox regression model within each centre will be extended to include an interaction term between the intervention group and (1) age (as a continuous variable), (2) baseline risk (continuous variable measured by the UKPDS CVD risk score). The interaction effects will then be pooled across centres using fixed effects meta-analysis, as in section 5.1. If the p-value for the pooled interaction effect is <0.05 , then the number and percentage of individuals with the endpoint within each randomised group, together with the intervention effect (and 95% CI) will be reported separately within categories defined by the subgroup variable. For age these will be <60 and ≥ 60 years, and for baseline risk, the cut-off for the categories will be the sex-specific median of the risk score at baseline. The hazard ratio at the cut-off will also be reported, together with how it changes per 10 year increase in age (or per unit increase in baseline risk).

6.5 Multiplicity

In assessing the effectiveness of the intervention, a p-value will only be calculated for the comparison of the primary (composite) outcome between the randomised groups. For all other outcomes, including intermediate outcomes, the intervention effect will be reported together with a 95% confidence interval. Interpretation of results for individual components of the primary outcome will be cautious and results that are significant in isolation will be interpreted less strongly than sets of results that are mutually supportive, or which support corresponding primary outcomes, or which are supported in previous research findings.

p-values will also be calculated to assess the interaction between randomised group and pre-specified covariates (see section 6.4 Subgroup Analysis).

7 Timescale

All data from CRFs will be entered and cleaned by the end of Mar 2010. Endpoints will be finalised by the end of April 2010. Results are required for a planned symposium at EASD in Sep 2010.

8 References

White IR, Thompson SG. Adjusting for partially missing baseline measurements in randomized trials. *Statist. Med.* 2005;24:993-1007.

Gooley TA, Leisenring W, Crowley J, Storer B. Estimation of failure probabilities in the presence of competing risks: new representations of old estimators. *Statist. Med.* 1999;18:695-706.