IMPROVE trial statistical analysis plan

6th March 2013

1. Overview of Analyses and Manuscripts

The following provides the statistical analysis plans for the IMPROVE trial. The purpose is (i) to clarify the primary analyses, and (ii) to avoid misleading inferences that would arise from post-hoc analyses. Thus the statistical analysis plan has been drawn up in advance of looking at the outcome data.

This document describes the analyses that will be undertaken; split primarily by short-term outcomes and longer-term outcomes. Manuscripts will be prepared for both sets of outcomes, with descriptive statistics and analyses following the structure set out in this document.

Regarding time-lines for analysis and reporting the main features are:

- Recruitment of the 600 patients is expected to continue until August 2013 (at latest).
- Short-term outcome analyses (see Section 3) will be conducted once all patients have been followed-up for 1 month, and after the database has been cleaned. This analysis is expected to report in the Autumn/Winter of 2013.
- For patients randomised in 2013, patients may not have a full year of follow-up by the time long-term outcomes are reported (see Section 4) due to restrictions dictated by the end of the study grant. The database will be `paused' in January 2014 to facilitate the long-term outcome analysis. However, patients will remain flagged with MRIS and collection of follow-up data will continue after this period.
- A GANTT chart showing the agreed targets is given in **Figure 1**.

2. Background to the IMPROVE trial

The principal research question to be addressed by the trial is as follows:

"Can a strategy of preferential endovascular repair (EVAR) of ruptured Abdominal Aortic Aneurysm (AAA), versus the current practice of open repair, significantly reduce the 30-day mortality of ruptured AAA?"

The study is a multi-centre randomised controlled trial conducted in emergency departments in the UK and Canada.

2.1 Inclusion/Exclusion criteria

Patients who are moribund, those with known connective tissue disorders (e.g. Marfan syndrome), or those with a known previous AAA repair are ineligible to participate in the trial. Patients transferred from other hospitals with a diagnostic CT scan are eligible, provided their suitability for EVAR is not assessed before randomisation. There are no formal age limits for inclusion.

2.2 Consent

For patients who meet the eligibility criteria, informed consent is taken from either the patient (written or verbal), a relative/guardian/carer, or through the Mental Capacity Act (in England and Wales only).

2.3 Randomisation and Blinding

Randomisation is to either a **strategy of preferential endovascular repair (EVAR)** or to **normal care with open repair**. The strategy of endovascular repair necessitates rapid access to CT angiography to confirm rupture and determine anatomical suitability. Patients found to be not anatomically suitable to EVAR will undergo open repair. Patients randomised to normal care with open repair may still undergo a CT scan if considered important. Palliation is an option for either arm if a patient's health deteriorates rapidly after randomisation. Patients are individually randomised using a variable block size design stratified by centre (hospital). There is no blinding in this trial due to the operative procedures involved. However,

accumulating data on the primary outcome (mortality) and secondary outcomes by treatment group is only viewed by the trial statistician and the independent Data Monitoring Committee.

2.4 Study variables and endpoints

(i) Each centre provides information on patients not randomised into the trial (overall number, reasons for exclusion).

(ii) For randomised patients baseline data are collected for a variety of characteristics, including

Demographic and admission data

- Age, sex, post code, method of AAA rupture diagnosis, acute myocardial ischaemia (as assessed from an ECG), loss of consciousness during care episode, biological markers at admission (blood pressure, haemoglobin, creatinine), day and time of randomisation.

Information from CT scanning (if patient is sent for CT scan)

- Arrived alive in CT scan, time of arrival, blood pressure on arrival, confirmation of rAAA, suitability for EVAR. Furthermore, a DICOM copy of all CT scans are sent to the trial centre at Imperial College for further assessment of AAA morphology (including neck length, angulation and aortic diameter at lowest renal artery) at a core laboratory at St George's Vascular Institute. A random sample of CT scans and those with AAA reported locally as non-ruptured are reviewed by Ray Ashleigh in Manchester to confirm/refute the diagnosis of rupture by a specialist radiologist.

Operation data

- Arrived alive for aneurysm repair, blood pressure on arrival, compliance to randomised treatment (actual operation performed), anaesthesia, EVAR graft type, staffing, and other measurements relevant for economic analysis (such as theatre time, amount of blood products used).

Post-operation data

- Critical care resources for primary admission, Re-interventions/other interventions in primary admission

Hospital discharge for primary admission

- Date of death if not discharged alive, date of discharge, discharge to home/other care facility.

Patients are then followed-up for

- Death through linkage with the Medical Research Information Service (MRIS) [UK only], hospital records, and direct contact tracing.
- Critical care resources for each subsequent admission.
- Re-interventions relating to AAA
- Quality of life (at 3 months and 1 year post-operation), using EuroQol and "Health Services" questionnaires.
- CT scan (at 3 months for EVAR patients)

Derived variables

- Hardman Index (scored from 0 to 5 with one point for each of the following: aged >76, serum creatinine >190μmol/L, haemoglobin <9g/dL, electrocardiographic ischaemia, loss of consciousness after presentation).
- Lab-based definition of EVAR suitability as defined as the categorical variable of being either within or without liberal manufacturer's Instructions For Use (IFU). This definition derives from Schanzer A et al, Circulation 2011. For within liberal IFU, the following anatomical requirements must be met: maximum aneurysm neck diameter at lowest renal artery 32mm, minimum aneurysm neck length 10mm, maximum aneurysm neck angulation 60^{o}. This definition is acceptable to the majority of trial investigators.

2.5 Sample size

We will randomise 600 patients, half to open repair and half to CT scan followed by EVAR if anatomically suitable. The trial, comparing the groups as randomised, has 90% power to detect (as significant at 5%) a difference in 30-day mortality of 14%. This is based on estimated 30-day mortalities of 47% and 21% for patients receiving open repair and endovascular repair respectively, an estimate of 55% of patients being anatomically suitable

for EVAR after CT scan and that 5% of both randomized groups will not have ruptured AAA (identified only after randomisation). The estimated mortality is 44.6% in the open repair group and 30.4% in the EVAR first strategy group.

3. Short-term Outcomes Statistical Analysis Plan for paper I: autumn/winter 2013

3.1 Descriptive analyses of randomised patients

(i) A detailed CONSORT diagram describing patient flow with exclusions and total numbers randomised to each treatment. A few patients (7 to date) have been randomised in error, these will be described as fully as is possible and the Data Monitoring Committee asked to adjudicate as to whether these patients should be included or excluded from the analysis: this will be reported. The surgical procedure actually received (if any), and 30-day mortality numbers will be summarised within the CONSORT diagram. **Figure 2** shows the type of CONSORT diagram that will be presented.

(ii) Baseline comparability of randomised groups.

- Tables of summary statistics will be produced by randomised group for a number of baseline variables; age (continuous), sex, admission blood pressure (continuous), admission haemoglobin (continuous), admission creatinine (continuous), acute myocardial ischaemia as assessed from an ECG (binary), loss of consciousness (binary), Hardman index (integer score from 0 to 5). **Appendix I** shows templates of the tables that will be produced.
- Continuous variables will be summarised using the following statistics; n (non-missing sample size), mean, standard deviation, median, minimum, and maximum. The number of missing observations will also be reported.
- The frequency and percentages (based on the non-missing sample size) of observed levels will be reported for all categorical measures. The number of missing observations will also be reported.

(iv) CT scan data by randomised group; occurrence of CT scan, blood pressure on arrival, summary of CT findings (AAA confirmed, rupture observed, suitability for EVAR). **Appendix II** shows templates of the tables that will be produced. These are not baseline data as generally they are assessed after randomisation so the groups will not necessarily be balanced.

(v) Core-lab findings as assessed via DICOM images will be cross-tabulated with findings from hospital CT scan (rupture confirmed, AAA diameter, suitability for EVAR as per 2.4 above). These are not baseline data as generally they are assessed after randomisation so the groups will not necessarily be balanced. **Appendix III** shows templates of the tables that will be produced.

(vi) Surgical data will be summarised by randomised group. The type of operation received, adherence to randomised treatment (cross-overs), and reasons for cross-over will be categorised and reported together with the time from randomisation to surgery and number of reinterventions within 30 days. **Appendix IV** shows templates of the tables that will be produced.

(vii) Mortality rates will be summarised by randomised group. This will include 30-day, in-hospital and 24-hour mortality. The initial short-term outcomes report will be produced potentially whilst some patients remain in hospital. For this report, the number of undischarged patients will be reported, which will be updated in the long-term outcome report (**Appendix V**). We will also report the following information by randomised group:

- location of in-hospital deaths;
- causes of death;

- 30-day mortality by in or out of hours randomisation (in-hours to be defined as 8am-4pm Monday – Friday).

(viii) Consent procedures will be tabulated by centre (**Appendix VI)**.

(ix) Disposal (place of discharge) will be summarised by randomised group amongst those discharged alive (discharge to home or another care facility) (**Appendix VII)**

3.2 Descriptive analyses of non-randomised patients
Contextual information will be given describing patient characteristics (age, sex, procedure) and 30 days mortality statistics for non-randomised patients identified via HES at all participating trial hospitals.

3.3 Primary Outcome Analyses

1. *Primary Analysis*
The primary analysis will be a comparison of **30-day (all cause) mortality** between the randomised groups, following an intention-to-treat policy (ITT). A 2x2 table will be produced (**Appendix V**), accompanied by Pearson's chi-square test without continuity correction and associated p-value. The estimated odds ratio and absolute risk difference between randomised groups will be presented along with their 95% confidence intervals (assuming normality). A p-value less than 0.05 will be used to judge a statistically significant difference between the randomised groups.

2. *Adjustment for baseline Hardman index*
The primary outcome (30-day mortality) will be adjusted age (continuous), sex and baseline Hardman index (treating it as a continuous variable) in a secondary analysis, using logistic regression, providing an adjusted odds ratio and 95% CI. A sensitivity analysis, which includes centre as a random effect will also be undertaken by fitting a generalised mixed model.

3. *Subgroup analyses*
A limited number of predefined subgroups will be compared using logistic regression with a test of interaction, only for the primary outcome (30-day mortality). The chosen subgroups are
- Age (continuous)
- Gender
- Hardman Index (continuous)

Results will be shown by category (binary variables) or split at the median (continuous variables) for the purpose or presentation. Since three interaction tests will be performed, a p-value of <0.01 will be used as a guide before claiming strong evidence of differences between subgroups.

4. *Excluding non rAAA patients*
A sensitivity analysis will exclude patients found not to have a ruptured AAA (by local diagnosis) from the **primary outcome (30-day all-cause mortality)**. A 2x2 table will be produced, accompanied by Pearson's chi-square test and associated p-value. The estimated difference in proportions will be presented along with a 95% confidence interval (assuming normality).
It has been agreed that a more specialised report will be produced to investigate further exploratory analyses of the morphology of patients found to have rAAA. This will be separate from the short-term outcomes report. However, for the purposes of this report, summary statistics of morphology in patients with diagnosed rAAA will be presented (see section 3.1v) and the casual effect of EVAR versus Open repair on 30-day mortality will be assessed in those with an rAAA, both overall and by IFU guidelines (see Section 3.3.5).

5. *Non-compliance (cross-over) analysis*

We will conduct an analysis estimating the causal effect of EVAR versus Open repair on the **primary outcome (30-day mortality)** in a complier population, whilst respecting the randomisation (Cuzick J *et al.* Stat. Med. 1997). This should provide a better estimate of the true treatment effect without suffering from potential biases seen in a per-protocol analysis. Those patients who had no operation (palliated) or did not have an AAA rupture operation will be excluded from the analysis under the assumption that their outcome would be the same no matter what group they were randomised to. Patients who had a converted operation (EVAR converted to Open) will be treated as compliers if randomised to EVAR and non-compliers if randomised to Open.

Within a non-compliance analysis, we will also assess the causal treatment effect in those defined "suitable for EVAR" (lab based definition of within liberal IFU as defined in 2.4 above) on the 30-day mortality outcome. It is likely that over 90% of all patients will receive a CT scan to allow this subgroup to be defined, although analysis will be restricted to those individuals who have a core lab diagnosis of rAAA.

3.4 Secondary endpoint analyses

1. *Mortality*

The following secondary ITT mortality analyses will be undertaken

- **24-hour mortality**
- **In-hospital mortality**

The analysis for 24-hour mortality will present the estimated difference in proportions accompanied by a 95% confidence interval (assuming normality) and a p-value (calculated using Pearson's chi-square test).

In-hospital mortality will be analysed using time-to-event methodology, censoring those still alive in hospital at the time of database lock for the short-term outcomes analysis (one month after last randomisation). A competing risks set-up is appropriate for this outcome, since individuals discharged alive are informatively censored (at a lower risk than those still in hospital for the same length of time). We will therefore either set event times for those discharged alive to infinity to ensure they never have the event of interest (in-hospital mortality) or use a Fine and Grey competing risks model with the two competing events being death and discharge. The analysis will be considered preliminary, and a full analysis of in-hospital mortality will be conducted in the long-term outcome report (Section 4).

2. *Time to discharge*

Time to discharge will also be compared between the randomised groups within the short-term outcomes report. Two separate analyses will be considered:

1. Those who die in hospital will have their event time ("discharge") set to infinity. Patients who are still alive and in hospital at the time of database lock will be treated as censored data.
2. A Fine and Grey competing risks model will be considered, as above, with the two competing events being death and discharge.

In addition, time to discharge will be subdivided into separate analyses for time to discharge home and time to discharge to other care facility. Censoring for death before discharge and discharge to another destination will be accounted for using either approach 1) or 2) described above.

3.5 30-day cost analysis (see dummy tables listed)

i) The cost analysis will take a hospital perspective and will be limited to inpatient costs incurred between the date of randomisation and day 30. We will report the 30 day resource use (time in theatre, LOS in ICU and in hospital), and accompanying costs. Unit

costs will be taken from manufacturers' list prices (prostheses costs), local finance departments (staffing costs), by inflating EVAR I costs (consumable costs) and from English NHS reference prices (ICU costs). For each randomised arm, means will be reported according to ITT. In the base case, the incremental costs will be reported as unadjusted difference in means with 95% CI assuming Normality.

We will run the following sensitivity analyses (SA):
ii) As per the analysis of the main clinical outcomes, we will run regression analyses adjusting for baseline differences, and allowing for random centre effects.
iii)We will consider alternative regression models (e.g. GLMs with gamma distributions, with identity and log-link)
iv) We will make alternative unit cost assumptions (e.g assume alternative staffing levels in the operating theatre for costing either eEVAR or open repair)
iv) While Canadian and Scottish centres will be included in the main analysis they lack reference costs and will be excluded in the sensitivity analysis
v) Exclude non rAAA patients
vi) Allow for non compliance (cross-over analysis) as above. Specifically we will estimate the incremental costs of eEVAR versus open for those patients who have a CT scan and meet the criteria for eEVAR. We will use randomisation as an instrumental variable.

We will run the subgroup analysis as above: for age, gender, Hardman Index and Suitability, Again recognising that multiple comparisons are being made.

3.6 Handling of missing data

1. The primary outcome analysis should be subject to little or no missing data as mortality information is flagged through MRIS for England, Wales and Scotland. For Canadian centres, all attempts will be made to fully obtain information on 30-day mortality as a minimum for each patient.
2. Missing data that occurs in other outcomes, covariates or subgroup variables will be multiply imputed in the primary analysis to increase precision of the estimates and to avoid potential biases from a complete case analysis. Sensitivity analyses will be conducted to assess the impact of the multiple imputation and a complete case analysis will also be conducted. All imputations will be examined to ensure sensible values are being generated. Imputation models will contain baseline variables, outcome variables, and variables used to define subgroups.

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4. Long-term Outcomes Statistical Analysis Plan for paper II: April 2014

4.1 Descriptive analyses

Descriptive analyses will be presented as described in the short-term outcome plan (Section 3.1), with in-addition:

(i) Mortality rates will include updated in-hospital mortality status and 1-year mortality (where known) (**Appendix VIII**). A tabulation of the causes of death (as agreed by an end-point committee) will also be shown.

(ii) Critical care resources (number of days spent in intensive care, high dependency and routine ward) and re-intervention rates will be presented by randomised group (**Appendix IX**).

4.2 Secondary endpoint analyses

1. *Mortality*

The following secondary ITT mortality analyses will be undertaken

- **One-year mortality (all cause)**
- **One-year mortality (AAA related)**

Since some patients will not have been followed-up for a full one year, we will consider a time-to-event analysis for the one-year mortality outcome, censoring patients at their end of follow-up time, or at one year, whichever comes first. A comparison between groups will be made using the log-rank test and Kaplan-Meier survival curves will be plotted. AAA-related mortality will also be investigated using a log-rank test, with patients who die from other causes censored at their date of death.

2. *Other analyses*

The following analyses will also be conducted and compared between the randomised groups within the long-term outcomes report:

1. In-hospital mortality
2. Time-to-first re-intervention
3. Rate of re-interventions within the first 12 months

In-hospital mortality will be reported in this long-term outcome analysis using the updated information on patients who were still in hospital at the time of the short-term analysis Similar methodology will be used as reported for the short-term outcome paper (Section 3.4).

Time-to-first re-intervention will be compared between the randomised groups using the log-rank test and Kaplan-Meier survival curves will be plotted. Deaths that occur before re-intervention will be treated as censored data.

In addition the rate of re-interventions within the first 12 months of follow-up will be compared between the randomised groups using Poisson regression with follow-up time as an offset

4.3 One year cost-effectiveness analysis

This will be undertaken in conjunction with the analysis of one year clinical outcomes, in early 2014. We will report the mean EQ-5D at 90 days and at one year. For those patients observed to survive up to one year, QALYs will be calculated using the EQ-5D scores at 90 days and one year, and assuming an EQ-5D score of zero at baseline. For survivors we will then calculate QALYs using linear interpolation across these three timepoints (see also SA). For decedents we will assume zero QALYs.

The cost analysis will take a hospital and personal social services perspective. We will report resource use (including re-interventions and hospital readmissions covering major comorbidities such as stroke and MI). We will calculate total cost at one year.

Those patients randomised in 2013 will not have the requisite information on one year survival, EQ-5D or cost. This will be handled by using Inverse probability weighting to handle the censoring. For the remaining patients, any missing EQ-5D or resource use data will be handled with multiple imputation.

The base case analysis will report the incremental effects of randomisation to eEVAR versus open, with bivariate regression models that allow for correlation between costs and health outcomes assuming bivariate Normality.

We will report incremental effects as mean differences (95% CI) in:

- EQ-5D at each timepoint
- one year QALY
- total costs.

Cost-effectiveness will be reported as incremental net benefits by valuing QALY gains at £20,000 and £30,000 per QALY, and by calculating cost-effectiveness acceptability curves.

We will repeat the above sensitivity analyses, and in addition we will consider:

a) Alternative assumptions concerning QALYs for the decedents and the linear interpolation for the survivors (e.g. rather than assuming that the survivors had an EQ-5D of zero at baseline use linear interpolation from the 30 day EQ-5D, or apply the 30 day EQ-5D at baseline)
b) Including cases randomised in 2013. Use multiple imputation to impute survival status and EQ-5D and costs at 1 year, conditional on predicted survival.

We will repeat the previous subgroup analyses.

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5 Lifetime CEA for HTA report only (analysis to also be completed by April 2014, for report due date June 2014)

This will be completed by 30th April 2014, in time for final deadline for HTA report (July 2014). Lifetime CEA requires information on long-term survival, QOL and cost of alternative interventions. It will be necessary to make assumptions about the long-term prognosis of IMPROVE patients based on the maximum duration of survival data collected in the study, but also drawing on evidence from the literature. The cost analysis will take an NHS and social services perspective. In extensive sensitivity analyses, we will test whether the results are robust to alternative assumptions. We will take an approach that predicts QALYs and costs for each individual patient.

a) Survival

For each patient randomised we will calculate total survival time up to death or 31st December 2013. We will plot Kaplan-Meier survival curves showing deaths from any cause over time until the last available timepoint. We will follow methodological guidance and consider alternative parametric approaches for extrapolating the observed survival (NICE 2008, Latimer).

When considering alternative parametric specifications we anticipate excluding the first 30 days of follow-up, as during this time period, patients will have relative high risks of death; and it may be judged inappropriate to use this portion of the data for predicting the long-term probability of death. We will compare the relative goodness of fit of the alternative parametric survival functions, for the remaining period of observed survival according to the Akaike Information Criterion (AIC) and Bayesian Information Criterion (BIC).

We will assess the relative plausibility of the survival predicted by the alternative extrapolation approaches from 6 months up to 4 years, by comparison with the all cause death rates from:

i. The observed data in the IMPROVE trial
ii. the age-gender matched general population
iii. previous studies with longer-term follow-up (e.g. Noorani et al, 2012, Johnston 1994. Norman et al 1998).

In the base case we will select the extrapolation approach judged the most plausible. For example, it may be that a Weibull extrapolation is the most plausible up to 2 years post randomisation and then after this it may be judged most appropriate to apply an age-gender matched general population life-expectancy for each individual for their remaining life expectancy.

A key issue is whether the extrapolation approach assumes that any differences in all cause mortality at one year are maintained. The base case analysis will assume that differences in survival at one year are maintained, but this assumption will be challenged in subsequent sensitivity analyses.

b) QALYs

In the base case analysis, we will compare the EQ-5D scores with those of the age-gender matched general population. We will conduct a linear interpolation assuming that any decrement in QOL attenuates over time such that after 5 years, the QOL is that of the age-gender matched general population. This approach would also assume that any differences between the randomised arms in QOL reported at one year attenuate over time (see SA). After five years we assume that the QOL is that of the general population.

c) Costs

No cost information is collected after one year, but it is recognised that costs attributable to rupture may be maintained over time, and that any differential survival may influence incremental costs.

We will use information from the one year cost analysis to project costs over time. For those observed to survive at one year we will calculate the hospital and community care costs incurred between month 3 and 12. We will then use the costs observed over this 9 month period to predict the hospital and community care costs incurred between months 12 and 24 for those individuals predicted to survive at month 24. To consider the costs of deaths between years one and two, we will calculate an average cost for a patient who dies between months 3 and 12 and apply this average cost to those observed or predicted to die between months 12 and 24.

After 24 months we propose assuming that no further hospital costs are incurred that are attributable to the rupture, but we will continue to apply annual community service costs to those predicted to survive at years 3,4 and 5. After 5 years we will assume no further costs (see SA).

All costs and QALYs accrued after one year will be discounted at rates recommended by NICE.

The base case analysis will again report the incremental effects of randomisation to eEVAR versus open, with bivariate regression models that allow for correlation between costs and health outcome assuming bivariate Normality. Cost-effectiveness will be reported as incremental net benefits by valuing QALY gains at £20,000 and £30,000 per QALY, and also by calculating cost-effectiveness acceptability curves.

Sensitivity analysis

In addition to the preceding SA we will consider the following alternatives:

a) Rather than taking an approach that assumes that any differences in survival after 12 months are maintained we will assume that there are no differences in survival after 12 months
b) We will take the alternative extrapolation approaches that are judged the next most plausible. For example, if the base case analysis applies a Weibull function for months 12-24 and then assumes general population death rates we will consider i) Applying a Weibull extrapolation for a longer duration (e.g. 5 years) b) Other parametric approaches e.g. Gompertz, c) More flexible alternatives e.g. piecewise hazard functions
c) For HRQOL, we will consider other assumptions including, no differential HRQOL between the arms after one year, that the HRQOL decrement versus the general population is maintained until 5 years, and alternative durations for the decrement e.g. 2 years, 10 years.
d) For the costs, we will consider the possibility that after rupture higher hospitalisation costs are maintained for 5 years, and that community care costs are maintained for up to 10 years.

The previous subgroup analyses will be repeated.

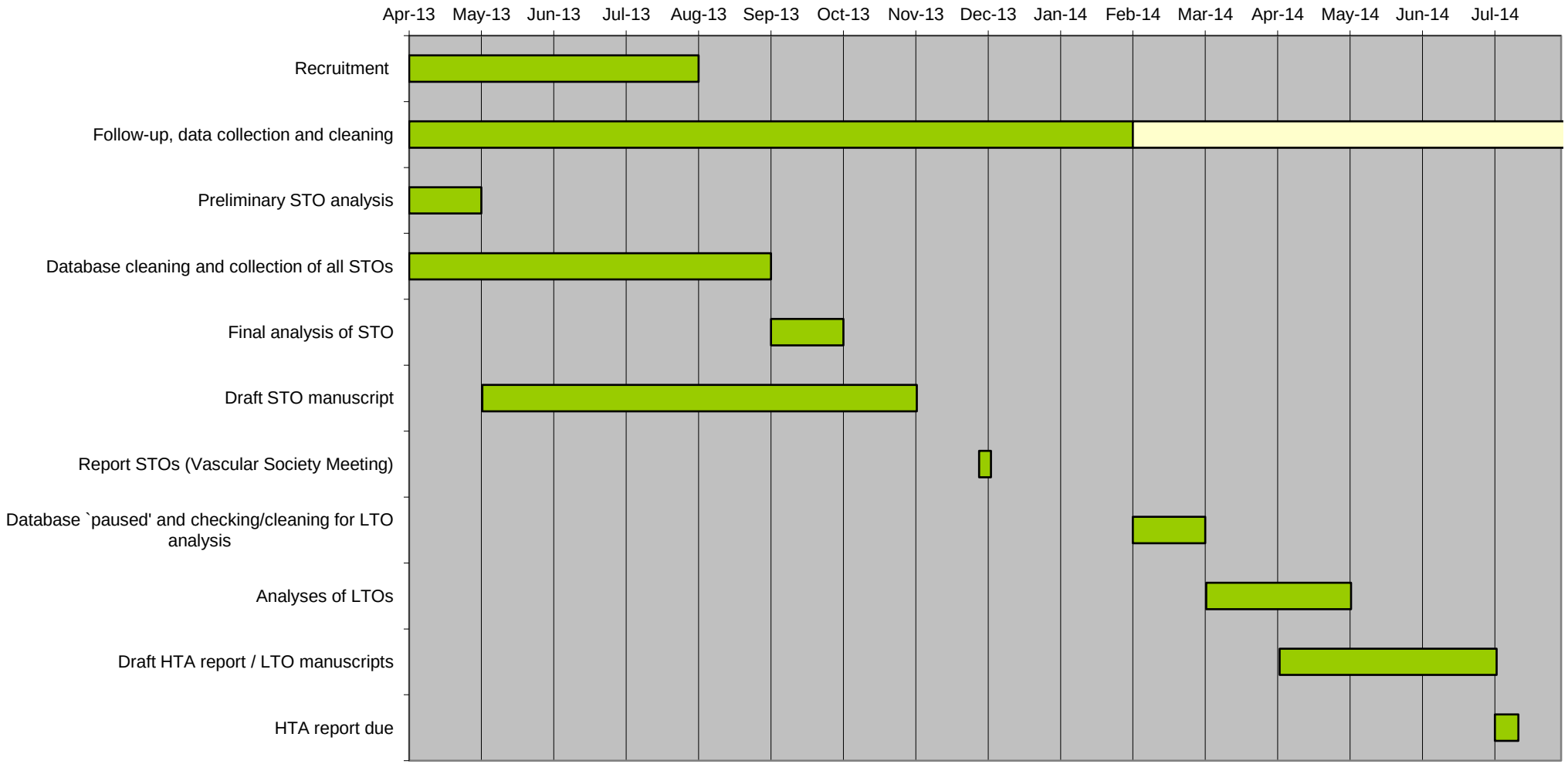

Figure 1. GANTT chart showing expected timeline for analysis and reporting of the IMPROVE trial. Extended follow-up and data collection will continue after the main analyses and report for the long-term outcomes (yellow shaded bar)

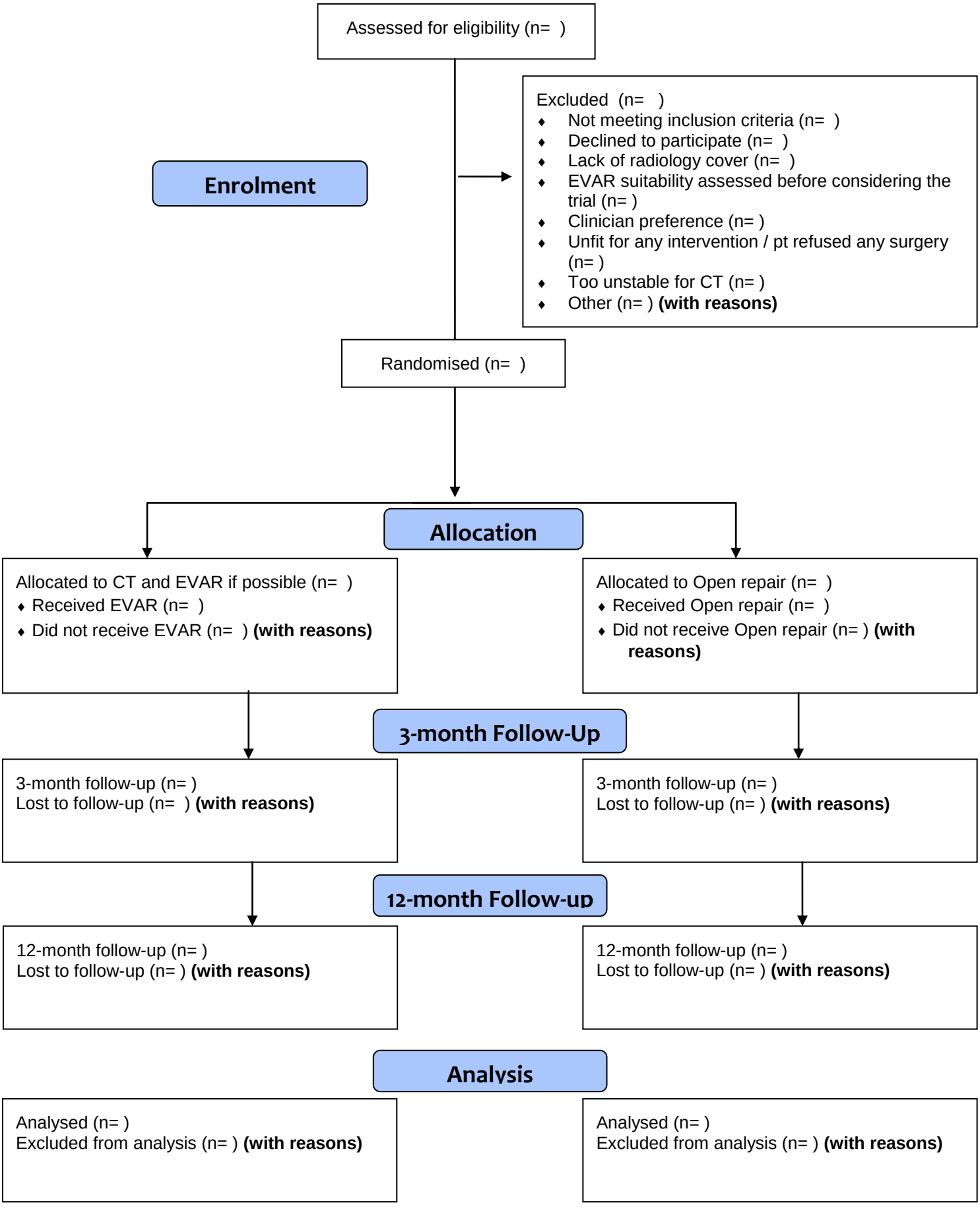

Figure 2. Example CONSORT diagram for patient flow through the trial

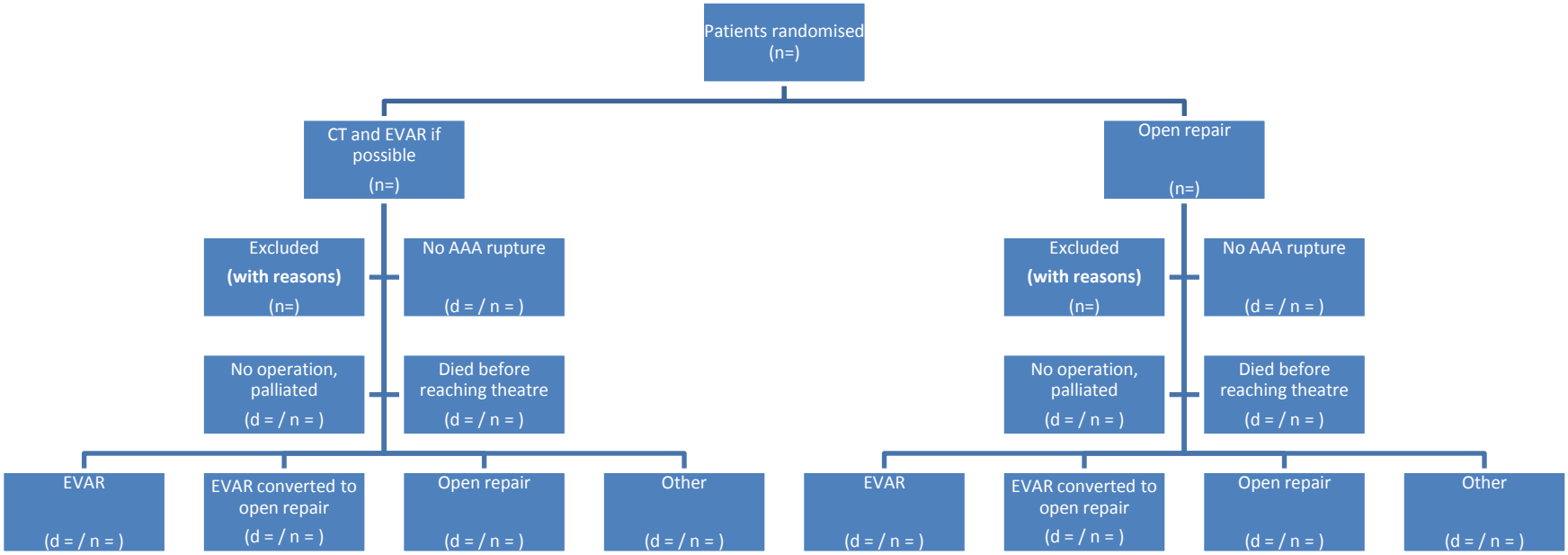

Figure 3. Example CONSORT diagram of surgical interventions including 30-day mortality rates
[d is the number of deaths within 30-days at each stage, n is the number of patients at each stage]

Appendix I: Template of descriptive tables to be presented for baseline variables in short-term outcome analyses (STOs).

Age at randomisation	CT and EVAR if possible	Open repair
Age (years)	n, m, sd, med, min, max [nmiss]	n, m, sd, med, min, max [nmiss]

n = non-missing sample size, m = mean, sd = standard deviation, med = median, min = minimum, max = maximum, nmiss = number missing covariate information

Sex	CT and EVAR if possible	Open repair
Male	n (%)	n (%)
Female	n (%)	n (%)
Missing	nmiss	nmiss

nmiss = number missing covariate information

Admission blood pressure	CT and EVAR if possible	Open repair
Systolic blood pressure (mm Hg)	n, m, sd, med, min, max [nmiss]	n, m, sd, med, min, max [nmiss]
Diastolic blood pressure (mm Hg)	n, m, sd, med, min, max [nmiss]	n, m, sd, med, min, max [nmiss]

n = non-missing sample size, m = mean, sd = standard deviation, med = median, min = minimum, max = maximum, nmiss = number missing covariate information

Admission haemoglobin	CT and EVAR if possible	Open repair
Haemoglobin (g/dl)	n, m, sd, med, min, max [nmiss]	n, m, sd, med, min, max [nmiss]

n = non-missing sample size, m = mean, sd = standard deviation, med = median, min = minimum, max = maximum, nmiss = number missing covariate information

Admission creatinine	CT and EVAR if possible	Open repair
Creatinine (micromol/l)	n, m, sd, med, min, max [nmiss]	n, m, sd, med, min, max [nmiss]

n = non-missing sample size, m = mean, sd = standard deviation, med = median, min = minimum, max = maximum, nmiss = number missing covariate information

Acute myocardial ischaemia	CT and EVAR if possible	Open repair
Yes	n (%)	n (%)
No	n (%)	n (%)
Missing	nmiss	nmiss

nmiss = number missing covariate information

Loss of consciousness	CT and EVAR if possible	Open repair
Yes	n (%)	n (%)
No	n (%)	n (%)
Missing	nmiss	nmiss

nmiss = number missing covariate information

	CT and EVAR if possible	Open repair
Hardman index 0	n (%)	n (%)
Hardman index 1	n (%)	n (%)
…		
Hardman index 5	n (%)	n (%)
Missing	nmiss	nmiss

nmiss = number missing covariate information

Appendix II: Template of descriptive tables to be presented for CT scan findings in short-term outcome analyses (STOs).

Received CT scan	CT and EVAR if possible	Open repair
Yes	n (%)	n (%)
No	n (%)	n (%)
Missing	nmiss	nmiss

nmiss = number missing covariate information

Blood pressure on arrival in CT suite	CT and EVAR if possible	Open repair
Systolic blood pressure (mm Hg)	n, m, sd, med, min, max [nmiss]	n, m, sd, med, min, max [nmiss]
Diastolic blood pressure (mm Hg)	n, m, sd, med, min, max [nmiss]	n, m, sd, med, min, max [nmiss]

n = non-missing sample size, m = mean, sd = standard deviation, med = median, min = minimum, max = maximum, nmiss = number missing covariate information amongst those who have CT scan

AAA confirmed	CT and EVAR if possible	Open repair
Yes	n (%)	n (%)
No	n (%)	n (%)
Missing	nmiss	nmiss

nmiss = number missing covariate information who have CT scan

Rupture observed	CT and EVAR if possible	Open repair
AAA Yes	n (%)	n (%)
AAA No	n (%)	n (%)
Other aneurysm Yes	n (%)	n (%)
Other aneurysm No	n (%)	n (%)
Missing	nmiss	nmiss

nmiss = number missing covariate information who have CT scan
Other includes rupture of thoracoabdominal, thoracic or common iliac aneurysm.

Local assessment for suitability of EVAR	CT and EVAR if possible	Open repair
Yes	n (%)	n (%)
No	n (%)	n (%)
Missing	nmiss	nmiss

nmiss = number missing covariate information who have CT scan

Appendix III. Descriptive tables of findings from core-lab DICOM images.

CT scan / core-lab	Rupture confirmed	
Rupture observed	Yes	No
Yes	n (%)	n (%)
No	n (%)	n (%)

CT scan / core-lab	Core-lab assessment of Suitability for EVAR* (for patients found to have rAAA)		
Local assessment of suitability for EVAR	Within stringent IFU	Within liberal IFU but outside stringent IFU	Outside liberal IFU
Yes	n (%)	n (%)	n (%)
No	n (%)	n (%)	n (%)

* within liberal IFU (Schanzer A et al Circulation 2011).

Suitability for EVAR* (for patients found to have rAAA)	CT and EVAR if possible	Open repair
Within stringent IFU	n (%)	n (%)
Within liberal IFU but outside stringent IFU	n (%)	n (%)
Outside liberal IFU	n (%)	n (%)

* within liberal IFU (Schanzer A et al Circulation 2011).

For patients found to have rAAA	CT and EVAR if possible	Open repair
AAA diameter (ultrasound)	n, m, sd, med, min, max [nmiss]	n, m, sd, med, min, max [nmiss]
AAA diameter (local CT)	n, m, sd, med, min, max [nmiss]	n, m, sd, med, min, max [nmiss]
AAA diameter (Core lab CT)	n, m, sd, med, min, max [nmiss]	n, m, sd, med, min, max [nmiss]

Appendix IV. Descriptive tables of findings of operation data.

Procedure received	CT and EVAR if possible	Open repair
EVAR: Tube Bifurcated Aortouni-iliac	 n (%) n (%) n (%)	 n (%) n (%) n (%)
Open repair	n (%)	n (%)
EVAR converted to Open	n (%)	n (%)
Other	n (%)	n (%)
No operation, palliated	n (%)	n (%)
Died before reaching theatre	n (%)	n (%)
No AAA rupture	n (%)	n (%)
Missing	nmiss	nmiss

Reasons for cross-over	Randomised EVAR, got Open	Randomised Open, got EVAR
Not anatomically suitable	n (%)	n (%)
Anaesthetist refusal to give GA	n (%)	n (%)
Patient request after randomisation	n (%)	n (%)
Other comorbidities	n (%)	n (%)
Medical fitness / rapid deterioration	n (%)	n (%)
Did not have CT scan / no radiographer present	n (%)	n (%)
None given	n (%)	n (%)

Time from randomisation to theatre/endovascular suite	CT and EVAR if possible	Open repair
Time (minutes)	n, m, sd, med, min, max [nmiss]	n, m, sd, med, min, max [nmiss]

No. reinterventions within 30 days	CT and EVAR if possible	Open repair
0	n (%)	n (%)
1	n (%)	n (%)
2	n (%)	n (%)
3+	n (%)	n (%)

Appendix V. Descriptive tables of mortality rates.

For those with confirmed diagnosis of ruptured aneurysm, or undergoing repair of an urgent or symptomatic aneurysm, all deaths within 30-days or in-hospital will be considered as aneurysm-related.

30-day mortality	CT and EVAR if possible	Open repair
Yes	n (%)	n (%)
No	n (%)	n (%)

In-hospital mortality	CT and EVAR if possible	Open repair
Yes	n (%)	n (%)
No	n (%)	n (%)
Still remain in-hospital	n (%)	n (%)

24-hour mortality	CT and EVAR if possible	Open repair
Yes	n (%)	n (%)
No	n (%)	n (%)

Location of in-hospital deaths	CT and EVAR if possible	Open repair
Before arrival to theatre/endovascular suite (including those palliated)	n (%)	n (%)
In-theatre	n (%)	n (%)
After AAA repair	n (%)	n (%)
After non-aortic procedure	n (%)	n (%)

Causes of death of those without AAA	CT and EVAR if possible	Open repair
ICD10 coding from death certificate	n (%)	n (%)
...		

Appendix VI. Descriptive tables of consent procedures.

	Consent procedure			
Centre	**MCA (E&W only)**	**Relative / Guardian / Carer**	**Verbal (witnessed)**	**Written**
Centre 1	n (%)	n (%)	n (%)	n (%)
Centre 2	n (%)	n (%)	n (%)	n (%)
…	n (%)	n (%)	n (%)	n (%)
Centre m	n (%)	n (%)	n (%)	n (%)

Appendix VII. Descriptive tables of disposal (place of discharge) for those discharged alive.

	Place of discharge	
	CT and EVAR if possible	**Open repair**
Home	n (%)	n (%)
Another care facility	n (%)	n (%)
Missing	n (%)	n (%)

RESOURCE USE AND COST TABLES FOR 30 DAY ENDPOINT PAPER I
Main TABLES
Resource use within the first 30 days post randomisation

Resource use item	**CT and EVAR if possible**	**Open repair**
	Mean (SD)	**Mean (SD)**
Time in theatre (mins)		
Days in critical care		
Days on general medical wards		
Total hospital days		

Total and incremental costs within the first 30 days post randomisation

Resource use item	**CT and EVAR if possible**	**Open repair**	**Incremental costs**
	Mean (SD)	**Mean (SD)**	**Mean (95% CI)**
Procedure costs			
Critical care			
General medical costs			
Other costs			
Total costs			

Supplementary Tables
Unit costs (£):
- procedural costs: EVAR open repair
- Critical Care for each HRG
-General medical bedday costs

- sensitivity results: Figure showing incremental costs by scenario

- subgroup results: Figure showing incremental costs by subgroup

Appendix VIII. Additional descriptive tables of mortality rates for long-term outcomes report.

In-hospital mortality	CT and EVAR if possible	Open repair
Yes	n (%)	n (%)
No	n (%)	n (%)

Location of in-hospital deaths	CT and EVAR if possible	Open repair
Before arrival to theatre/endovascular suite	n (%)	n (%)
In-theatre	n (%)	n (%)
In-hospital (including those palliated)	n (%)	n (%)

1-year mortality	CT and EVAR if possible	Open repair
Yes	n (%)	n (%)
No	n (%)	n (%)
Still under follow-up	n (%)	n (%)

1-year mortality	CT and EVAR if possible	Open repair
Rate (per-person year)	n (%)	n (%)

Appendix IX. Descriptive tables of critical care resources and re-intervention rates.

Care resources, no. days	CT and EVAR if possible	Open repair
Intensive care	n, m, sd, med, min, max [nmiss]	n, m, sd, med, min, max [nmiss]
High dependency ward	n, m, sd, med, min, max [nmiss]	n, m, sd, med, min, max [nmiss]
Routine ward	n, m, sd, med, min, max [nmiss]	n, m, sd, med, min, max [nmiss]

Re-intervention in the primary admission	CT and EVAR if possible	Open repair
Yes	n (%)	n (%)
No	n (%)	n (%)

Rate of re-intervention in the first 12 months	CT and EVAR if possible	Open repair
Rate (per person-year)	n, m, sd, med, min, max [nmiss]	n, m, sd, med, min, max [nmiss]

Reasons for re-intervention	CT and EVAR if possible	Open repair
Control bleeding	n (%)	n (%)
Limb ischaemia	n (%)	n (%)
Mesenteric ischaemia	n (%)	n (%)
Abdominal compartment syndrome	n (%)	n (%)
Other	n (%)	n (%)

Subsequent hospital admissions	CT and EVAR if possible	Open repair
In-patient stay (days)	n, m, sd, med, min, max [nmiss]	n, m, sd, med, min, max [nmiss]

RESOURCE USE AND COST TABLES FOR 1 year ENDPOINT PAPER II

Main TABLES
Resource use within the first year post randomisation

Resource use item	CT and EVAR if possible	Open repair
	Mean (SD)	Mean (SD)
Index admission		
Time in theatre (mins)		
Days in critical care		
Days general medical wards		
Total hospital days		
N(%) Readmissions		
Days in critical care		
Days general medical wards		
Total hospital days		
Overall days in hospital		
Outpatient visits		
Community service use		

EQ-5D outcomes at 90 days and 1 year (needs to be conjunction with mortality)

EQ-5D for survivors	CT and EVAR if possible	Open repair
Mean (SD) EQ-5D, 90 days	n (%)	n (%)
Mean (SD) EQ-5D at one year	n (%)	n (%)

Cost-effectiveness at 1 year (needs to be conjunction with mortality)

	CT and EVAR if possible Mean (SD)	Open repair Mean (SD)	Incremental (95% CI)
Total one year costs	n (%)	n (%)	
Total QALYs at one year	n (%)	n (%)	
Net Monetary Benefits			

Total and incremental costs within the first year post randomisation

Resource use item	CT and EVAR if possible	Open repair	Incremental costs
	Mean (SD)	**Mean (SD)**	**Mean (95% CI)**
Procedure costs			
Critical care			
General medical costs			
Outpatient costs			
Community service costs			
Total costs			

Supplementary Tables/ Figures
Unit costs (£):
- procedural costs: EVAR open repair
- Critical Care for each HRG
-General medical bedday costs

Mean and incremental costs within one year post-randomisation, by subgroup
Cost-effectiveness at one year: incremental QALYs, costs and incremental net benefits, by subgroup
Sensitivity analyses
Cost-effectiveness acceptability curves

Cost-effectiveness tables/figures for HTA report

Will include:

LIFETIME RESULTS

Table: Lifetime cost-effectiveness analysis: mean (SD) costs (£), lifeyears, QALYs and incremental net benefits (£)

Table: Lifetime cost-effectiveness analysis: mean (SD) costs (£), lifeyears, QALYs and incremental net benefits (£): by subgroup

Cost and cost-effectiveness

Figure: Sensitivity analysis reporting mean total costs at 30 days post randomisation according to alternative assumptions

Figure: Sensitivity analysis reporting mean incremental net benefits at one year post randomisation according to alternative assumptions

Figure: Cost effectiveness (CEACs) for one year post randomisation

Figure: Kaplan Meier survival curves

Figure: Comparison of alternative parametric extrapolations for survival from 12 months to five years post randomisation

Figure: Lifetime cost-effectiveness analysis: Cost effectiveness (CEACs)

Figure: Sensitivity analysis reporting lifetime incremental net benefits (£) according to alternative assumptions

Figure: Sensitivity results showing incremental costs by scenario

Figure: Subgroup results showing incremental costs by subgroup