Analysis plan for clinical and cost-effectiveness analyses at 3 years after randomisation

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Overview

This analysis will be undertaken when all randomised patients after have reached the 3 year time-point (end July 2016). The analysis will be of three year clinical outcomes- survival and aortic-related re-interventions, and cost-effectiveness. The cost-effectiveness endpoints will be: incremental life years, QALYs, costs, and net monetary benefits at 3 years.

For each repair strategy, this will involve the estimation of the effect of randomised arm on:

- all-cause mortality and aneurysm-specific mortality with all available follow-up at time of database lock. This will be a minimum of 3 years for all patients and a maximum of 7 years.
- aneurysm-related re-interventions, using all available follow-up.
- health-related quality of life (EQ-5D) at 3 years
- aneurysm-related resource use and costs up to three years

We will then contrast the endovascular strategy versus open repair according to the intention-to-treat (ITT) principle, by reporting Incremental costs, life years, QALYs, costs per QALY and incremental net monetary benefits. These results will be reported overall, and for previously pre-defined subgroups. The subgroups have been ranked in order of importance by the clinicians on the Trial Management Committee as 1. sex, 2. Hardman index, 3. aneurysm neck length and 4. lowest systolic blood pressure.

1. Clinical endpoints

a. Survival

A time-to-event analysis will be conducted with Kaplan Meier survival curves plotted and a comparison between randomised groups made using the log-rank test. For this analysis all available follow-up will used. Patients will be censored at the time ONS mortality flagging was last accessed, or for patients without ONS flagging at the last time of local clinical follow-up. Survival probabilities in each of the randomised groups will be estimated from the Kaplan Meier curves at the 3-year time point post-randomisation. The proportional hazards assumption will be assessed using Schoenfeld residuals. If this is satisfied then unadjusted and adjusted hazard ratios together with their 95% confidence intervals will be estimated using a Cox proportional hazards model. The adjusted hazard ratio will account for age, sex, baseline Hardman index, lowest systolic blood pressure on day of admission and aneurysm neck length, with missing values multiply imputed. If the proportional hazards assumption is violated then we will further estimate hazard ratios in two follow-up time epochs, acute and mid-term (e.g. between 0-3months and >3 months to 3 years of follow-up). A sensitivity analysis will be performed restricting the population to those with a final diagnosis of ruptured AAA.

All analyses will then be repeated for aneurysm-specific mortality. Aneurysm-specific mortality will be defined as all deaths within 30 days of randomisation for patients diagnosed as having a ruptured aneurysm; for any later deaths within 30-days of an elective repair (for patients without rupture on admission) or following rupture in patients with other primary admission diagnoses, secondary rupture following aneurysm repair, and

within 30 days of any readmission for an aneurysm-related re-intervention. Patients who die from other causes will be censored at their date of death.

In calculating incremental life years and QALYs we will use all-cause mortality in the main analysis, and aneurysm-specific mortality in a sensitivity analysis. The use of aneurysm specific mortality may lead to small gains in precision, as 'other cause' mortality would be pooled across the trial arms including that for patients without any diagnosis of AAA. This will require life years gained to be calculated by adjusting the cause-specific survival function for the mean other-cause mortality pooled across both randomised arms, rather than using randomised group-specific estimates of other cause mortality. This approach makes the assumption that randomised arm has no effect on 'other causes' of death [Kim L, Thompson SG, Health Economics 2011;20:842-52].

b. Aneurysm-related re-interventions

The type and number of re-interventions will be documented and tabulated by randomised group by time epoch since randomisation, an example of which is shown in Table B. A comparison of the time until first aneurysm-related re-intervention will be made by fitting Kaplan-Meier curves and calculating the log-rank test statistic. Deaths that occur before re-intervention will be treated as censored data. All available follow-up for re-interventions will be used, with patients censored at the time that HES data was last accessed or the last date of clinical audit/monitoring, whichever is latest. The main 2 categories of re-interventions in mid-term will be arterial and the rate of re-interventions will also be compared between the randomised groups using a repeated events survival model (e.g. the Anderson-Gill proportional hazards model). Both unadjusted and adjusted analyses will be produced (adjusting for age, sex, Hardman index, aneurysm neck length and lowest systolic blood pressure on day of admission). The effect of aortic morphology on re-intervention type and rate also will be assessed in a separate analysis (see 2 below).

c. Subgroup and sensitivity analyses for clinical endpoints

We will consider a limited number of predefined subgroup analyses, based on baseline characteristics, for the clinical endpoint all-cause mortality at 3 years. Further subgroup analysis for quality of life and for assessing cost-effectiveness also will be conducted (see Section 2.). Specifically the chosen subgroups are 1) sex, 2) Hardman index (continuous), 3) aneurysm neck length and 4) lowest systolic blood pressure on day of admission. An interaction test within a logistic regression model will be used to assess the effects of the specified subgroups. Since four 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.

As stated above, one proposed sensitivity analysis is to restrict the analysis population to patients with diagnosed rAAA only. We will also estimate a complier average causal effect of the IMPROVE trial policy (EVAR if anatomically suitable vs. Open repair) for the 3 year (all-cause) mortality outcome only.

2. Effect of aortic morphology on reinterventions

This investigation will comprise a separate chapter of the HTA report and other publication of the results considered as appropriate. The study population for these analyses is defined as all patients randomised in the IMPROVE trial with a confirmed diagnosis of a ruptured aorto-iliac aneurysm, who had a pre-operative CT scan and who received an operation (EVAR, Open repair or EVAR converted to Open). Patients in the IMPROVE trial whose final diagnosis was not rupture (e.g. symptomatic AAA who receive a semi-elective procedure) will therefore be excluded from these analyses. Ruptured iliac aneurysms will be included, except for the analyses based on maximum common iliac diameter. Patients will be analysed according to the operation that was commenced and so are observational comparisons and not comparisons by randomised group.
The re-interventions will be categorized as either arterial (those relating to directly to the abdominal aorta, visceral and distal run off arteries) or laparotomy-related (eg incisional hernia repairs, abdominal procedures following from compartment syndrome, mesenteric or colonic ischaemia etc) or other.
The main outcome will be arterial re-intervention within 3 years of randomisation, with a secondary outcome of all re-interventions within 3 years, since data from Hospital Episode Statistics to cross-check the results reported from trial centres will only be available for 3 years following the date of initial patient discharge. However, as previously all available follow-up information also will be used.
The morphological features assessed will be as previously (Eur Heart J 2015): these are a) aortic neck length, b) aortic neck diameter at the distal renal artery, c) maximum AAA diameter, d) neck conicality e) proximal aortic neck α-angulation, f) maximum common iliac diameter (but here excluding patients with ruptured iliac aneurysms).

Each of these variables will be treated as continuous covariates in the regression models. Time from randomisation to an arterial (or any) re-intervention will be modelled using an Anderson-Gill repeated events proportional hazards model. All analyses will be adjusted as previously described. Hazard ratios will be presented for each variable based on a 1 standard deviation increase to allow a fairer comparison of the relative importance of each morphological variable.

All continuous morphology variables will be initially assumed to have a linear relationship with the log-hazard for the outcome of interest. However, we will also consider non-linear effects of the morphological variables by using multivariable fractional polynomials with variable selection techniques (Sauerbrei and Royston, JRSS A 1999). Any non-linear relationships identified will be plotted and assessed for biological plausibility.

3. Quality of life and cost endpoints

a. EQ-5D and QALYs up to 3 years

EQ-5D
We will report the mean EQ-5D at 3 months, 1 and 3 years, by randomised arm, for those patients alive at each time point, and for all patients randomised. This approach maintains

the ITT estimand used in the primary analyses of mortality at 3 years, and recognises that patients who die are assigned an EQ-5D of zero from the time of death. Subgroup analyses will be conducted, as for the clinical variables, using multiple imputation for missing values.

QALY

We will combine the EQ-5D with the survival data to report QALY at 3 years, which will require assumptions to be made in the base case, which will be challenged in subsequent sensitivity analyses. We will initially use all the EQ-5D data that we have, irrespective of the time when it was actually recorded. In practice, due to the project extension to allow the reporting of 3-year outcomes not being fully approved until mid-September 2013, the final quality of life questionnaire was completed between 2.8 and 4.0 years after randomisation.

QALYs up to 3 months

For those patients who survive up to 3 months, QALYs up to 3 months will be calculated using the EQ-5D scores at 3 months, assuming an EQ-5D score of zero at randomisation, and a linear interpolation between randomisation and 3 months. This implies that at day 30, EQ-5D is approximately one third of the EQ-5D at 3 months (see Figure 1). For decedents between randomisation and 3 months, we will assume zero QALYs. Individuals without ruptured AAA will be initially assumed to have the mean baseline EQ-5D of elective EVAR patients (taken from the EVAR 1 trial as listed in the HTA report).

QALYs 3 months to 1 year

For those surviving up to 12 months, we will assume a linear interpolation, using the EQ-5D scores at 3 months and one year. For decedents between 3 months and 12 months where an EQ-5D score at 3 months is available, a linear interpolation will be applied between the 3 month EQ-5D, and the date of death when a zero EQ-5D score will be applied (see also section on missing data).

QALYs 1 year to 3 years

For those surviving up to 3 years, we will again assume a linear interpolation, using the EQ-5D scores at 1 year and 3 years. For decedents between 1 year and 3 years, where an EQ-5D score at 1 year is available, a linear interpolation will be applied between the 1-year EQ-5D, and the date of death when a zero EQ-5D score will be applied.

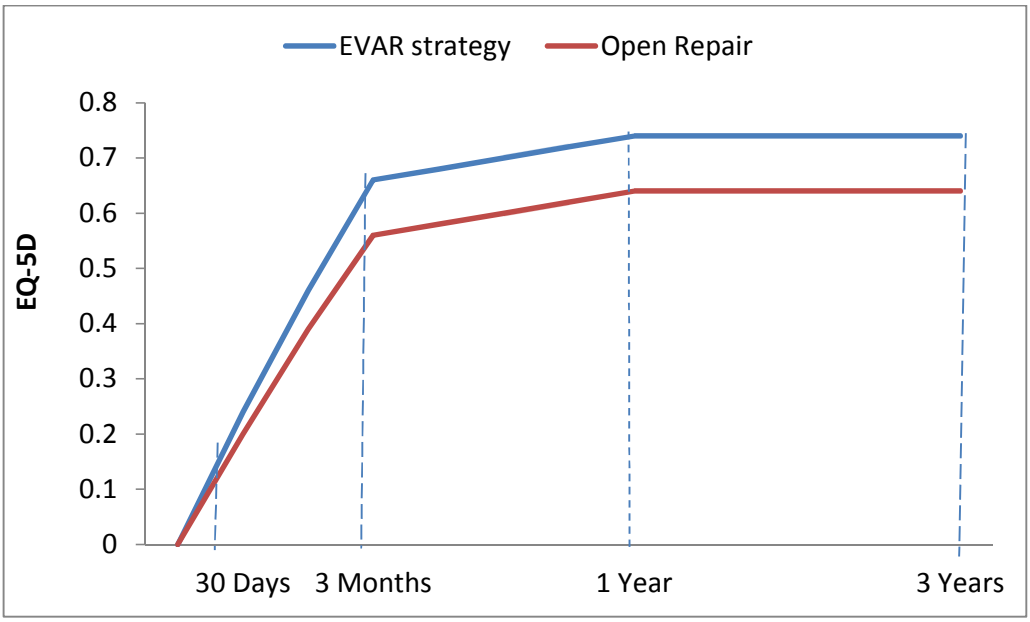

Figure 1. Example of 3-year QALY by using linear interpolation between randomisation, the 3-month, 1-year and 3-year time points when EQ-5D data were collected

b. Costs

We will calculate total aneurysm-related cost to three years for all patients randomised.

The cost analysis will take a hospital. The primary sources of the resource use data will be the IMPROVE CRFs, completed with use of HES data. We will include the total length of stay (LOS) for hospitalisations within the primary admission (CRFs 5). We will also report resource use for re-admissions (7 and 8), including re-interventions (CRFs 6). Re-interventions will include the additional cost of theatre time and consumables. Data on re-admissions, including re-interventions and potential complications for patients with ruptures, will be extracted from the CRFs, and from Hospital Episode Statistics (HES) data. The data from HES will be used to provide a cross-check on aneurysm-related re-interventions from the CRFs, and to identify hospital admissions for other causes in both trial and non-trial hospitals. The use of hospital readmission data from 3 sources (CRFs, patient questionnaires, and HES) is designed to avoid missing hospital episodes (for example from non-IMPROVE centres), but raises the possibility of double-counting (see sensitivity analysis).

Unit costs will be taken from those previously collated for the 1-year analysis, plus recommended sources such as PSSRU for outpatient visits, and community service use.

4. Lifetime survival, QOL and costs

Such analyses will be contingent on the 3-year analyses and remain highly speculative in the absence of data on mortality, re-interventions and quality of life to 3 years. Patients in the IMPROVE study had their vital status followed up until July 2016, and all available follow up will be used. For each patient the total survival time will be calculated up to death or the time ONS mortality status was last accessed. As per the analysis of clinical endpoints, we will plot Kaplan-Meier survival curves showing the number of patients who died until the last available time point. We will then consider alternative parametric approaches for extrapolating the observed survival. This will exclude the first 3 months of follow up as the risk of death was very high, and hence, this portion of the survival data is not appropriate to predict long-term survival. We will compare the survival predicted by each parametric curve with that for the age-gender matched general population, to help identify the most plausible survival function.

To our knowledge there are no studies reporting long-term QOL in patients following repair of ruptured AAA. Thus, our estimates of lifetime QOL for each treatment group will be based on 3-year data from the IMPROVE trial. Initially, we will consider that the differences in QOL between arms at three years are maintained over time (see sensitivity analysis).

Estimates for long-term costs will also be based on the costs collected in the IMPROVE trial and HES data. We will focus on inpatient costs resulting from re-admission (including re-interventions. The base case analysis will make the conservative assumption that after three years there will be no further re-admissions and re-interventions attributable to the initial ruptured aneurysm.

5. Statistical analysis for cost-effectiveness

The base case analysis will report the incremental effects of randomisation to an endovascular strategy versus open repair. We will use bivariate regression models that allow for correlation between costs and health outcomes assuming bivariate Normality.

We will initially report incremental effects as mean differences (95% CI) in EQ-5D (3 months, one year, and three years), and life years, QALY and total costs all at three years. We will then report lifetime costs and QALYs, discounted at recommended rates for England (3.5%), based on the assumptions described in the previous section. Cost-effectiveness will be reported as ICERs (incremental costs per life year and per QALY) and incremental net benefits by valuing QALY gains at £20,000 and £30,000 per QALY, and by calculating cost-effectiveness acceptability curves.

Missing EQ-5D at 3 months, 1 year and 3 years, and missing total cost data at 3 years will be handled with multiple imputation, assuming data are missing at random. Note this imputation approach will not be applied to the non-rAAA patients, as these will be different according to unobserved factors, and so for these patients we will apply EQ-5D and costs from the EVAR 1 study (see sensitivity analysis). As per the analysis of clinical endpoints at three years, we will conduct pre-specified subgroup analyses as for the clinical analyses.

6. Sensitivity analysis for cost-effectiveness

The sensitivity analyses will include those pertaining to:

QOL measurement

- alternative assumptions for the QoL of individuals with no rAAA, for example assume the same EQ-5D as that of age-matched general population.
- Alternative assumption about EQ-5D between 3 months and 1 year and 3 years that all decedents have zero QALYs
- For the lifetime analysis, we will assume that the QOL differences attenuate over time. We will predict the mean QOL for each treatment arm between 3 and 10 years, assuming a linear interpolation, such that after 10 years the mean QOL was that of the age-matched general population.

Costs

- Alternative assumptions on costs for the individuals with no AAA operation. For example, we will consider they stay half of the hospital stay in critical care and the other half in general medical wards. An alternative would be to use mean within-hospitals over one year from elective EVAR patients (EVAR 1, HTA report).
- consider concern that may have double-counted inpatient costs across the two sources, by excluding inpatient costs from i) HES

Mortality

CEA endpoints will use aneurysm-specific not all-cause mortality at three years, after adjusting to allow for the competing risk of non-cause specific mortality.

Statistical analysis

- A model to recognise potential clustering, e.g. bivariate random-effects model
- Alternative distributional assumptions for both cost (e.g. Gamma) and QALY (e.g. Gamma in 3-QALYs scale).

Change of estimand

As per the main clinical, analysis, we will restrict the population of interest to patients with diagnosed rAAA only. We will also estimate a complier average causal effect of the cost-effectiveness of the IMPROVE trial policy (EVAR if anatomically suitable vs. Open repair), and of receipt of EVAR versus Open using randomisation as an instrumental variable.

Flexibility

The results may dictate additional analyses which cannot be specified at this time.

Cost-effectiveness modelling

7. Illustrative Example Tables and Figures

Table A: Cause of death between 90-days and 1 year

Cause of death	EVAR strategy	Open repair
AAA		
Myocardial disease		
Stroke & other vascular disease		
Pulmonary disease		
Renal disease		
Cancer		
Other		

Table B Re-interventions

Re-intervention	EVAR strategy	Open repair
Randomisation to 90 days	**N=**	**N=**
Control of bleeding	**n (%)**	**n (%)**
Limb Ischaemia	**n (%)**	**n (%)**
Mesenteric ischaemia	**n (%)**	**n (%)**
Abdominal compartment syndrome	**n (%)**	**n (%)**
Endoleak correction	**n (%)**	**n (%)**
Type I		
Type II		
Type III		
other		
Graft thrombosis	**n (%)**	**n (%)**
Other (specified)	**n (%)**	**n (%)**
Other (unspecified)	**n (%)**	**n (%)**
91 days to 3-years	**N=**	**N=**
Arterial*	**n (%)**	**n (%)**
Laparotomy-related*	**n (%)**	**n (%)**
Other (unspecified)	**n (%)**	**n (%)**

*details provided elsewhere, including reinterventions for endoleaks after EVAR

Table C. Resource use up to three years after randomisation Mean (SD) unless stated

Resource use item	EVAR strategy	Open repair
Primary admission		
Time in theatre (mins)		
Days in critical care		
Days on general medical wards		
N (%) Re-interventions		
Total days		
Convalescent care- days in nursing home days in cottage hospital		
Re-admissions*		
N (%) re-admissions		
Days in critical care		
Days on general medical wards		
N (%) re-interventions		
Total days		
Total hospital LOS up to 3 years		

*Data on re-admissions taken from the CRFs and HES questionnaires.

Table D. Unit costs

Table E. Total and incremental costs up to three years after randomisation

Cost component	EVAR strategy	Open repair
	Mean (SD)	Mean (SD)
Primary admission		
Devices & consumables		
Theatre time		
Critical care stay		
General medical care		
Re-interventions		
Re-admissions		
Theatre time		
Critical care		
General medical care		
Total cost		

Table F. Mean (SD) Outcomes at 3 months, and 3 years, overall and by subgroup

Outcome	EVAR strategy	Open repair
Mortality		
N (%) all cause deaths, 3 months		
N (%) aneurysm-specific deaths, 3 months		
N (%) all cause deaths, 3 years		
N (%) aneurysm-specific deaths, 3 years		
Life-years (all randomized patients)		
EQ-5D for ruptured AAA survivors		
3 months		
3 years		
QALY (3 years)		
Ruptured AAA survivors		
Ruptured AAA survivors and deceased		
All randomised patients		

Table G. Lifetime costs, QALYs, incremental cost-effectiveness ratios (ICER), and incremental net monetary benefit (INB).

	EVAR strategy Mean (SD)	**Open repair** Mean (SD)	**Incremental [95% CI]**
Total costs			
Total life years			
Total QALYs			
ICER			
INB			

Figure A. Survival curves to 3 years by randomised group

Figure B. Time to first re-intervention up to three years by randomised group

Figure C. Cost-effectiveness acceptability curves (CEACs) for three years after randomisation

Figure D. Sensitivity analysis reporting mean incremental net benefits at three years after randomisation according to alternative assumptions, analyses and estimands

Figure E. Cost-effectiveness acceptability curves (CEACs) for three years after randomisation, by subgroup

8. Timelines (2016 unless stated)

- Finalise analysis plan, including clinical endpoints: September
- Availability of data for dry run of all endpoints for 1 year effectiveness and cost-effectiveness from CRFs, including EQ-5D: mid-October
- Preliminary analysis of 3 year costs, effectiveness and cost-effectiveness, with dummy analysis discussed by Writing Committee and full meeting required in early November.
- Data from Hospital Episode Statistics mid-October
- Audits at all sites complete by mid-October
- Final mortality flag from NHS digital: late-October
- Cleaning and cross-checking of Hospital Episode Statistics data early November
- Final data clean/lock late November
- Final run of all other main analyses: - late November/December
- Presentation of provisional 3-year results (mortality, re-interventions and quality of life) to Vascular Society 1st December
- Drafting of main paper, including cost-effectiveness data for mid-January 2017
- Aortic morphology analyses (midterm re-interventions & mortality) January 2017
- Close out processes (to be conducted remotely) - end of January/early February 2017
- Submission of manuscript(s): January/February 2017
- HTA report due 2 weeks after close of project, currently organised up to and including the 1 year results (suggested for end March 2017). However, the format of reports due in 2017 is changing, so additional time may be required to reformat the HTA report (e.g. mid-April 2017). The HTA report also will include a chapter on risk scoring.

9. Writing committee

Michael Sweeting, Richard Grieve, Manuel Gomes, Pinar Ulug, Simon Thompson, Rob Hinchliffe, Matt Thompson, Ray Ashleigh, Roger Greenhalgh, Janet Powell