IMPROVE trial: Analysis plan for clinical and cost-effectiveness analyses at one year post randomisation

Richard Grieve, Manuel Gomes, Michael Sweeting, Pinar Ulug, Janet Powell - 10th March 2014.

Overview

This analysis will be undertaken when all randomised patients after have reached the one year time-point (end July 2014). The analysis will be of one year clinical outcomes- survival and aortic-related reinterventions, and cost-effectiveness. The cost-effectiveness endpoints will be: incremental life years, QALYs, costs, and net monetary benefits at one year.

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

- aneurysm-specific and all-cause mortality up to one year.
- health-related quality of life (EQ-5D) at three months and one year
- Resource use and cost up to one year

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, for previously pre-defined subgroups (sex, age, Hardman index) and a sensitivity analysis restricted to patients with confirmed rupture who reached the operating suite alive.

1. Clinical endpoints

a. Survival up to one year

An analysis of all-cause survival rates at one year post randomisation will be conducted using a Pearson's chi-square test without continuity correction. Unadjusted and adjusted odds ratios together with their 95% confidence intervals will be estimated using logistic regression. The adjusted odds ratio will account for age, sex and Hardman index, with missing values multiply imputed. A further 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 follow-up will be curtailed (censored) at 1 year. A sensitivity analysis will be performed restricting the population to those with a final diagnosis of ruptured AAA who reached the operating suite alive.

All analyses will then be repeated for aneurysm-specific mortality at one year. 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 elective repair or following rupture in patients with other primary diagnoses or secondary rupture following aneurysm repair, and within 30 days of any readmission for an aortic-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 also makes the reasonable assumption that randomised arm has no effect on 'other causes' of death.

b. Re-interventions and AAA-related re-interventions

The type and number of re-interventions within the first year will be documented and tabulated by randomised group, an example of which is shown in Table B: these will be used for cost estimations. A comparison of the time until first AAA-related re-intervention will be made by fitting Kaplan-Meier curves and calculating the log-rank test statistic on the restricted population of patients who reached the operating suite alive. Deaths that occur before re-intervention will be treated as censored data. The rate of re-interventions within the first year will also be compared between the randomised groups using Poisson or Negative Binomial regression and with follow-up time as an offset. Both unadjusted and adjusted analyses will be produced (adjusting for age, sex and Hardman index).

c. Subgroup and sensitivity analyses for clinical endpoints

We will consider a limited number of predefined subgroup analyses for the clinical endpoint all-cause mortality at one year. Further subgroup analysis for quality of life and for assessing cost-effectiveness will also be conducted (see Section 2.). Specifically the chosen subgroups are 1) age (continuous), 2) sex, 3) Hardman index (continuous). An interaction test within a logistic regression model will be used to assess the effects of the specified subgroups. 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.

As stated above, one proposed sensitivity analysis is to restrict the analysis population to patients with diagnosed rAAA who reached the operating suite alive only. We will also estimate a complier average causal effect of the IMPROVE trial policy (EVAR if anatomically suitable vs. Open repair) for the 1 year (all-cause) mortality outcome only.

2. Quality of life and cost endpoints

a. EQ-5D and QALYs up to 1 year

<u>EQ-5D</u>

We will report the mean EQ-5D at 3 months and 12 months, 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 12 months, and recognises that patients who die are assigned an EQ-5D of zero from the time of death. Subgroup analyses for age, sex and Hardman's index will be conducted, as for the clinical variables.

<u>QALY</u>

We will combine the EQ-5D with the survival data to report QALY at 3 months and at 12 months, which will require assumptions to be made in the base case, which will be challenged in subsequent sensitivity analyses.

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). We will initially use all the EQ-5D data that we have at 3 months, irrespective of the time when it was actually recorded. 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 12 months

For those surviving up to 12 months, we will again 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). We will initially use all the EQ-5D data that we have at 3 and 12 months, irrespective of the time when it was actually recorded.

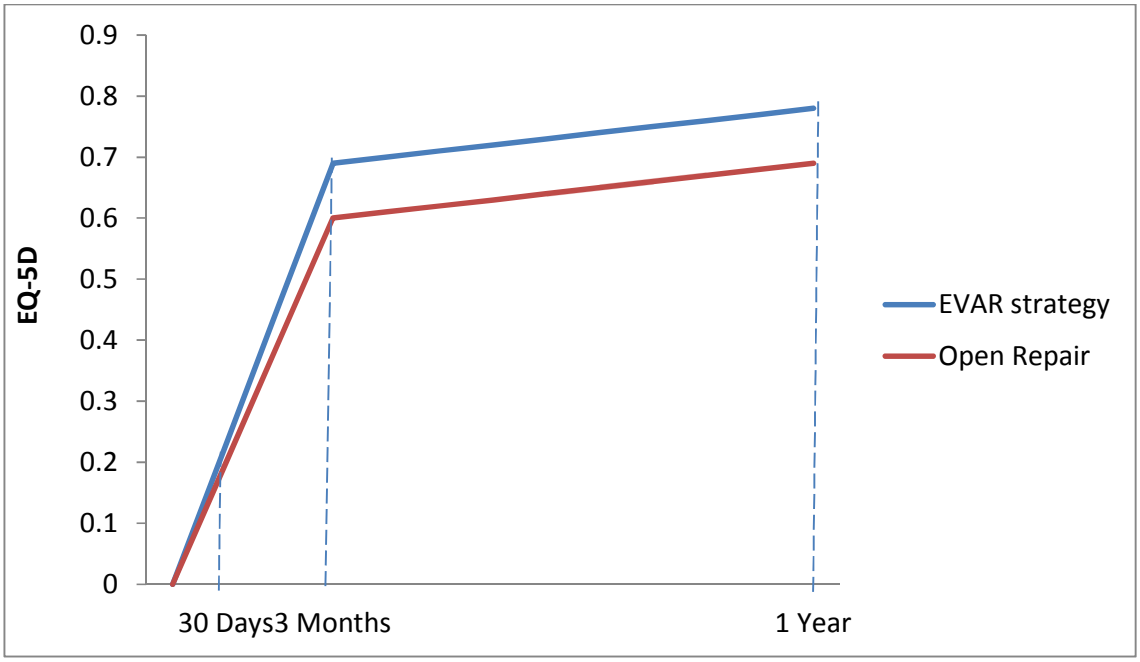

Figure 1 – 12 month QALYs by using linear interpolation between randomisation and the 3-month and 12 month timepoints when EQ-5D data were collected

b. Costs

We will calculate total cost at one year for all patients randomised.

The cost analysis will take a hospital and personal social services perspective. The primary sources of the resource use data will be the IMPROVE CRFs and individual patient questionnaires on the use of health services, completed with use of Hospital Episode Statistics for England (HES) data if possible[1]. We will include the total length of stay (LOS) for hospitalisations that were censored at 30 days, and censor all resource use at 12 months. We will report resource use for primary admission and re-admissions (CRFs 5, 7 and 8), including re-interventions (CRFs 6). Re-interventions will include the additional cost of theatre time. Data on re-admissions, including re-interventions and potential complications for patients with ruptures, will be extracted from the CRFs, if possible from HES, and from the patient questionnaires. The data from HES and the patient questionnaires will be used to provide a cross-check on AAA-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 upto 3 sources (CRFs, service use, 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).

The frequency of outpatient visits (CRFs 7 and 8), GP visits and other community care use will be considered from CRFs and from responses to service use questionnaires Individuals with no AAA will be assumed to stay in the general medical ward for the whole of their initial hospital episode. Information on readmissions for non-rupture patients may be available from HES (see sensitivity analysis). Unit costs will be taken from those previously collated for the 30 day analysis, plus recommended sources such as PSSRU for outpatient visits, and community service use.

c. 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 report incremental effects as mean differences (95% CI) in:

- EQ-5D at 3 months and one year
-life years at one year
- QALY at one year
- total costs.

[1] Following review of procedures no data from Hospital Episode Statistics have been available to academic researchers since May 2014. Footnote added 15th October 2014.

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 or 12 months, and missing total cost data at one year 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 also sensitivity analysis)

As per the analysis of clinical endpoints at one year, we will conduct pre-specified subgroup analyses according to age, gender and Hardman Index and sensitivity analyses for patients with confirmed ruptured AAA who reached the operating suite alive.

d. Sensitivity analysis for cost-effectiveness

The sensitivity analyses will include those pertaining to:

Endpoint measurement

QOL

- 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 assumptions about EQ-5D up to 3 months: i) that the QOL observed at day 90 was actually achieved at day 30; ii) that there were no QOL gains before 3 months
- exclusion from EQ-5D estimation- all those known to complete the questionnaire outside a window of 1 month after versus before the 3 or 12 months timepoint
- Alternative assumption about EQ-5D between 3 months and 12 months that all decedents have zero QALYs

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 three sources, by excluding inpatient costs from i) service use questionnaire ii) HES data if available

Mortality

- CEA endpoints will use aneurysm-specific not all-cause mortality at one year, 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. Two-part model).

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.

Illustrative Example Tables and Figures

Table A: Cause of death between 30-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 within 1 year

Re-intervention	**EVAR strategy** **N**	**Open repair** **N**
Control of bleeding	**n (%)**	**n (%)**
Limb Ischaemia	**n (%)**	**n (%)**
Mesenteric & colonic ischaemia	**n (%)**	**n (%)**
Abdominal compartment syndrome	**n (%)**	**n (%)**
Other: AAA-related	**n (%)**	**n (%)**
Minor procedure	**n (%)**	**n (%)**
Other (specified)	**n (%)**	**n (%)**
Other (unspecified)	**n (%)**	**n (%)**

Table C. Resource use within the first year post 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 1 year		
Community service use		
Outpatient visits		
GP visits		
Nurse visits		

*Data on re-admissions taken from the CRFs and Health Services use questionnaires and HES if possible.

Table D: unit costs

Table E. Total and incremental costs within the first year post 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		
Outpatient cost		
GP visits		
Nurse visits		
Total cost		

Table F. Mean (SD) Outcomes at 90 days and 1 year, 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, 12 months		
N (%) aneurysm-specific deaths, 12 months		
EQ-5D for survivors		
3 months		
12 months		
EQ-5D all patients		
3 months		
12 Months		

Table G. Costs, QALYs, incremental cost-effectiveness ratios (ICER), and incremental net monetary benefit (INB) at 1 year

	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 12 months by randomised group
Figure B: Time to first re-intervention up to 12 months by randomised group

Figure C: Cost-effectiveness acceptability curves (CEACs) for one year post randomisation

Figure D: Sensitivity analysis reporting mean incremental net benefits at one year post randomisation according to alternative assumptions, analyses and estimands

Figure E: Cost-effectiveness acceptability curves (CEACs) for one year post randomisation, by subgroup

Timelines (2014 unless stated)
-Finalise analysis plan, including clinical endpoints: mid-March 2014
-Availability of data for dry run of all endpoints for 1 year effectiveness and cost-effectiveness from CRFs, including EQ-5D and service use data: mid-March
-preliminary analysis of 3 and 12 month costs, effectiveness and cost-effectiveness April-August, with dummy analysis discussed by Writing Committee required in early July.
- Circulation of findings from dry run, and full meeting: early/mid September
- final data clean/lock end September
- dry run of HES analysis/ final run of all other analyses: October-December
- final mortality flag from information centre: October
- HES extraction resource use data: November, if data available
- Presentation of final results and drafting of paper: December/Jan 2015.
- submission of manuscript: December/January 2015

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