Ruptured aneurysm trials Individual Patient Data meta-analysis statistical analysis plan

12th June 2014 updated 24th July 2014 following data cleaning & merging

The following provides the statistical analysis plans for the individual patient data (IPD) meta-analyses of the trial reported to date: AJAX, ECAR and IMPROVE trials. **Unfortunately, the Nottingham trial has suffered data loss (no back up database) and there will be no data to contribute (RJ Hinchliffe, personal communication 15th January 2014).** 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 any outcome data.

1. Time-lines

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

- AJAX outcomes, short-term and to 1 year are available, May 2014.
- ECAR: short-term outcomes available to 1 year are available, June 2014.
- IMPROVE: short-term outcomes available, 3-month outcomes available April 2014, 1-year outcomes available August 2014.
- Data harmonisation will be conducted by Dr Pinar Ulug and is expected to take up to 3 months.
- Data sharing agreements are in place.
- Therefore no analyses could begin until July 2014
- Agreement from PIs to submit 3-month outcome data to AHA 2014
- All analyses should be completed by March 2015

2. Background to the trials and their different methodologies

Since these were surgical trials neither patients nor clinicians could be blinded to treatment given.

- The **Nottingham trial** was a single vascular centre early pilot trial, with 32 patients randomised 2002-4 (sealed envelopes), and mainly demonstrated the feasibility of running a trial for emergency surgery. The primary outcome was 30-day mortality. Early results were published in EJVES 2006;32:506-13
- The **AJAX trial** was a 3 vascular centre trial conducted around Amsterdam with 116 patients recruited between 2004 and 2011. All included patients were considered after CT scan to show both rupture and anatomical suitability for conventional EVAR and had relative haemodynamic stability, with randomisation using sealed envelopes. The primary outcome was combined morbidity and mortality at 30 days: 3 patients were found at operation not to have rAAA. Early results were published in Ann Surg 2013;258:248-56
- **ECAR** was a multicentre French trial with 107 patients recruited between 2008 and 2013. All included patients were considered after CT scan to show both rupture and anatomically suitability for conventional EVAR and had relative haemodynamic stability (mean arterial pressure ≥80 mm Hg), with allocation of treatment (open or endovascular) rotated on a weekly basis. The primary outcome was 30-day mortality. Results have been presented (Veith 2013, CACVS 2014 with reported 30-day mortality of 17% for EVAR and 25% for open repair) but publication not yet available.
- **IMPROVE trial** was a 30 centre trial (mainly UK), which recruited 613 patients with a clinical diagnosis of ruptured aneurysm between 2009 and 2013. Patients were randomised to either an endovascular strategy or open repair before the diagnosis and anatomical suitability for EVAR had been confirmed by CT scan, the trial included haemodynamically unstable patients and used an independent contractor for 1:1 telephone-computer randomisation: 55 patients did not have AAA as the cause of admission and a further 22 patients had a symptomatic unruptured AAA. The primary

outcome was 30-day mortality. Early results were published in BMJ 2014;348:f6771 and a cohort analysis of patients with rupture in Br J Surg 2014;101:216-224.

3 Study variables and endpoints

The common baseline data collected by the 3 trials with data are shown in Table 1.
The common operation data collected by the 3 trials are shown in Table 2
The common follow-up data are shown in Table 3.
Diagnostic CT scans and variables available are shown in Table 4

4. Scope

Scope: To provide best quality evidence concerning the management of **ruptured** abdominal aortic aneurysm (rAAA) from a European perspective.

5. General approach to IPD Analysis

The primary analyses will be by randomised group, irrespective of the different trial designs. Secondary analyses will be conducted at 2 levels with the purpose of making the groups in the different trials more homogeneous:

(a) After exclusion of non-AAA diagnosis and non-ruptured AAA patients from both IMPROVE and AJAX. ECAR reports only rAAA patients.
(b) As in (a) above but by further restricting IMPROVE patients to include only those considered locally as "suitable for EVAR" and back filling missing data with available information of "within liberal IFU" from core laboratory analysis.

The largest trial, IMPROVE, has described imputation of missing data and this will be used. Imputation has not been described for AJAX and ECAR and will not be applied to these data sets.

6. Specific aims

A To confirm or refute results published in the 2014 Cochrane review

B To assess the effect of the sub-groups age, sex and Hardman index on **30-day and 3 month mortality,** timed from date of randomisation for IMPROVE and ECAR, and date of admission for AJAX. In particular, to assess whether the effect of sex observed in the IMPROVE trial is consistent across the all the trials. Descriptive data, including baseline characteristics, brief operative data, complications/reinterventions and length of stay to be presented alongside this analysis. Data merging for complications/reinterventions from the 3 trials may prove very difficult or impossible.

C To assess the effect of **aortic morphology** on 30-day mortality and reinterventions after both EVAR and open repair. The sample sizes will be approximately 250 EVARs and 400 open repairs. The IMPROVE trial morphology statistical analysis plan will be followed for the 4 morphological parameters available across all 3 trials: maximum aortic diameter, neck diameter, neck length and proximal neck angle (see Table 4). The top aneurysm neck diameter is reported by ECAR and IMPROVE and the maximum neck diameter by AJAX. Descriptive data for aortic morphology in all trials will be presented.

D To assess **12 month outcomes** by subgroups as in B and C above and describe the major complications of EVAR or open repair to 12 months, with the purpose of identifying morphological, surgical or physiological criteria which influence their development eg age, aortic morphology, graft configuration, length of procedure.

E To assess cost-effectiveness of the two treatment strategies across the 3 recent European trials. The additional data needed for these analyses are shown in Table 5.

7. Publication strategy

Publications need to be agreed by the 3 Chief Investigators and acknowledge all investigators

A Early mortality and complications to 3 months – abstract submitted to AHA June 2014
B 12 month outcomes
C European Health economic perspective

Availability of data as per case record forms; to be updated once full data have been received from all 3 trials

Table 1

	Baseline Data	**IMPROVE**	**AJAX**	**ECAR**
	Time of arrival	yes	yes	yes
	Sex	yes	yes	yes
	DOB /Age	Yes	yes	yes
Hardman Index	Haemoglobin on admission	yes	yes	yes
	Creatinine on admission	yes	yes	yes
	Acute ischaemia on ECG	yes	yes	yes
	Loss of consciousness	yes	yes	yes
	Volume of IV fluid given	yes	yes	**no**
	CT scan performed	yes	yes	yes
	Lowest recorded systolic blood pressure before transfer to CT or theatre	yes	yes	**no**, admission bp only
	Lowest recorded diastolic blood pressure before transfer to CT or theatre	yes	yes	**no**, admission mean bp only
	Max aortic diameter	yes	yes	yes

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Table 2 Operative details

Operation data	**IMPROVE**	**AJAX**	**ECAR**
Date of operation	yes	no	yes
Time of arrival in theatre/endo suite	yes	yes	yes
Blood pressure on arrival: systolic and diastolic	yes	yes	**no**
Was supracoeliac balloon inflated?	yes	yes	yes
Type of anaesthesia General/local/both	yes	yes	yes
Procedure	yes	yes	yes
Graft configuration	yes	yes	yes
Graft manufacturer	yes	yes	yes
Volume of contrast used	yes	**no**	yes
Was fem-fem crossover also performed?	yes	yes	yes
Blood products used	yes	**no**	**no**
Clinicians present	yes	yes	**no**
Did patient leave theatre alive?	yes	yes	yes
Time out of theatre	yes	yes	yes
Destination after procedure (recovery, ITU, ward)	yes	yes	**no**

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Table 3

	Follow-up data	IMPROVE	AJAX	ECAR
30 day follow-up	Mortality	yes	yes	yes
	24h mortality	yes	yes	Yes – 24hrs and 48 hrs
	Total hospital stay - days	yes	yes	yes
	Use of ITU/HDU	yes	yes	no
	Date of discharge – length of stay	yes	yes	yes
	Destination after discharge, hospital, convalescence or home	yes	yes	yes
	Re-intervention in primary admission	yes	yes	Yes, date only
	-return to endovascular suite (date and time)	yes	**No**,location of re-intervention n/a	**No**,location of re-intervention n/a
	-treatment of coexisting condition unrelated to AAA (date and time)	yes	**no**	yes, date only
	-return to operating theatre for re-intervention (date and time)	yes	No,location of re-intervention n/a	No, location of re-intervention n/a
	-control bleeding	yes	**?**	yes
	-limb ischaemia	yes	yes	yes
	-mesenteric Ischeaemia	yes	yes	yes
	-abdominal compartment syndrome	yes	**no**	yes
	Other (give reason)	yes	yes	yes
Post 30-day follow-up	Mortality	Yes	yes-6 months, but need to obtain additional information about any lost to FU patients	yes- 6months and 1 year
	Number of re-interventions	Yes, to 3 yearsYes	yes – 6 months	yes- 6months and 1 year
	-re-intervention to support AAA repair	yes	yes	yes

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	-Adjunct Endovascular Procedure	yes	yes	yes
	-Conversion to Open Repair	yes	yes	yes
	-Adjunct Abdominal Surgery	yes	yes	yes
	-Distal angioplasty	yes	**?**	**?**
	-Distal surgery	yes	**?**	**?**
	-Other	yes	Yes	Yes
	-Number of outpatients visit (aneurysm related only)	yes	**No**	**No**
	-Inpatients stay – length of stay including ITU (aneurysm related only)	yes	yes	yes
	Health Resources use	Yes	**no**	**no**
	-number of GP visits related to aneurysm	yes		
	-number of district nurse visits	yes		
	-stay in convalescent /nursing home	yes		
	-number of social worker visits	yes		
	-number of home carer visits	yes		
	-time off work	yes		
	-support from family/friends	yes		
	-hospital appointments/stay not related to aneurysm	yes		
	Quality of life EQ5D	Yes 3m, 12m	Yes 30d, 3m, 6m	**no**

Availability of data as per case record forms; to be updated once full data have been received from all 3 trials

Table 4 CT variables for analysis

Trial	AJAX	ECAR	IMPROVE
Max diameter cm	√	√	√
Top neck diameter cm	Max neck diameter	√	√
*Bottom neck diameter cm		√	√
*Distance bottom neck diameter from lowest renal cm		√	√
Neck length cm	√	√	√
α-Neck angle	√	√	√
Maximum common iliac diameter cm	?	√	√

*To assess neck conicality

Table 5 Additional data for optimal cost-effectiveness analyses

Staff use in theatre

Open repair
Anaesthetist (consultant) _ _
Anaesthetist (registrar) _ _
Vascular Surgeon (consultant) _ _
Vascular Surgeon (registrar) _ _
*ODA (Grade 5) _ _
Scrub Nurse (Grade 6) _ _
Runner (Grade 5) _ _
House Officer (Level 2) _
2nd Nurse (Grade 5) _
2nd Runner (Grade 5) _
2nd surgeon (consultant) _
2nd surgeon (registrar) _

EVAR
Anaesthetist (consultant) _ _
Anaesthetist (registrar) _ _
Vascular Surgeon (consultant) _ _
Vascular Surgeon (registrar) _ _
*ODA (Grade 5) _ _
Scrub Nurse (Grade 6) _ _
Runner (Grade 5) _ _
Radiographer _ _
Radiologist (consultant) _ _
Radiology Nurse (Grade 6) _ _
2nd runner (Grade 5) _
Radiologist (registrar) _

*ODA=operating department assistant

Note 1) resource use in critical care in ECAR and AJAX is not measured in terms of no. of organs supported, so we will need local unit costs (able to reflect different levels of care intensity). I suspect this is not a problem for AJAX, but it may be difficult to obtain these in France.

Note 2) outpatient visit and community care (GP, nurse visits, etc) are not collected in ECAR/AJAX, so the analysis on inpatient hospital care.