Quality Risk Assessment and Quality by Design in Clinical Research

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Quality

"Quality" is the absence of errors that matter to decision making

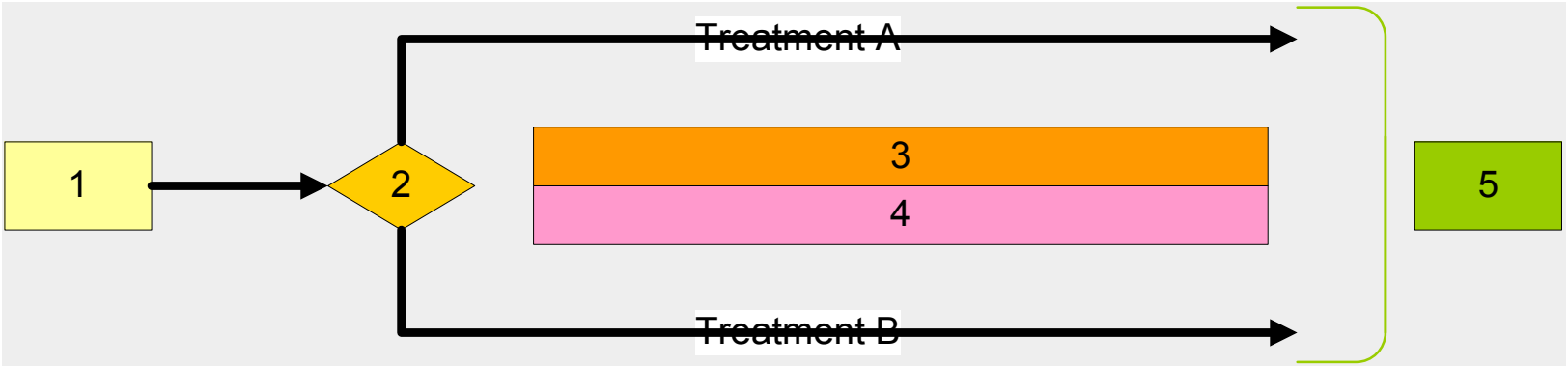
(i.e. errors that have a meaningful impact on patient safety or interpretation of results)

High quality clinical trials

Avoid errors that matter to decision making

* Human subjects protection
  * appropriate information & consent at each stage
  * safe administration & monitoring of investigational products
  * safe study procedures & investigations
* Reliability of results
  * Detect true effects (efficacy, safety)
* Wider environment
  * participants in other trials
  * public health (including patients not in trials)
  * physical environment

Reliable assessment of treatment effects



1	Recruitment
2	Randomization with Allocation Concealment
3	Compliance with allocated treatment
4	Capture of relevant events in appropriate detail
5	Analysis by allocated treatment

Impact of errors on the reliability of results

* **Random Errors**
  * affect the precision of estimates (adding "noise" and reducing statistical power), but will not introduce bias in either direction

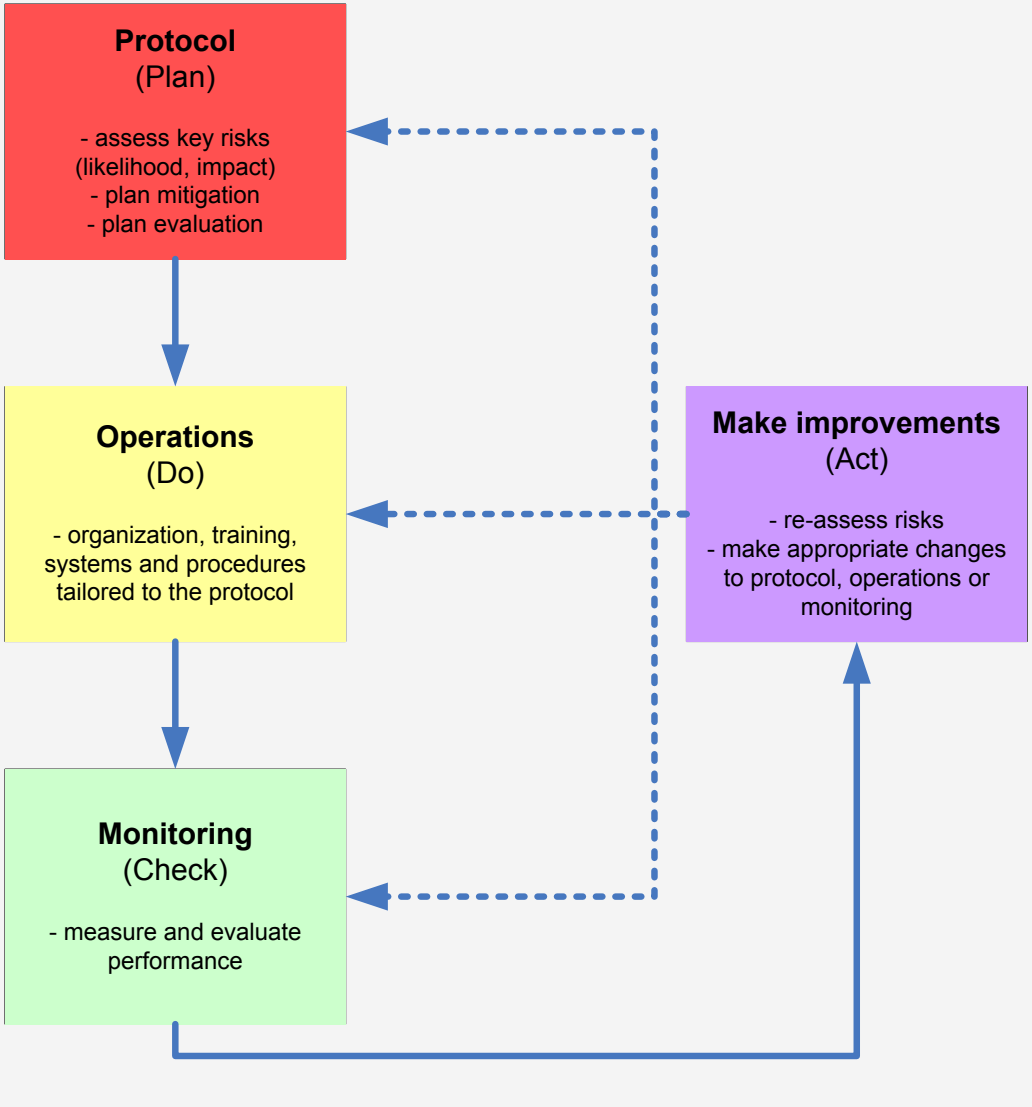
    [Note: For equivalence assessments, random errors are counter-conservative]

* **Systematic Errors**
  * lead towards a particular decision

Key features for reliable assessment of moderate treatment effects

- Proper randomization
  - no foreknowledge of likely treatment allocation
- Relevant outcomes
  - sufficient numbers
  - recorded with appropriate accuracy
  - adequate timescale
- Appropriate follow-up
  - meaningful treatment difference
  - minimize post-randomization withdrawals
  - minimize loss to follow-up (e.g. after 1st event occurs or study treatment stops)
- Unbiased ascertainment and analysis of study outcomes
  - focus on robustness of result, not precision of data points
  - comparisons with the randomized control group (except for assessing big effects on rare events)
  - avoid emphasis on subgroups and on non-randomized "on-treatment" analyses

Quality by Design (QbD)



Landray et al *DIJ 2012*

Facilitating recruitment

* Inclusion criteria
  * relevant to target population
  * at sufficient risk of the key outcomes
  * (not the same as participant characterization)
* Exclusion criteria
  * human subjects protection
    * focus on comorbidity, concomitant medication, consent
    * avoid unnecessary criteria
* Uncertainty principle
  * if uncertain whether the treatment is indicated (or contra-indicated), randomize
* Feasible
  * must fit with routine care: clinicians are busy, patients are sick

Compliance

* Clinical need always overrides research idealism
* Non-compliance
  * Active group doesn't receive / stops investigational device
  * Active group starts other treatment (e.g. effective comparator)
  * Control group receives investigational device
* Impact on results
  * less difference between randomized groups
  * conservative for superiority assessments
  * counter-conservative for non-inferiority / safety assessments

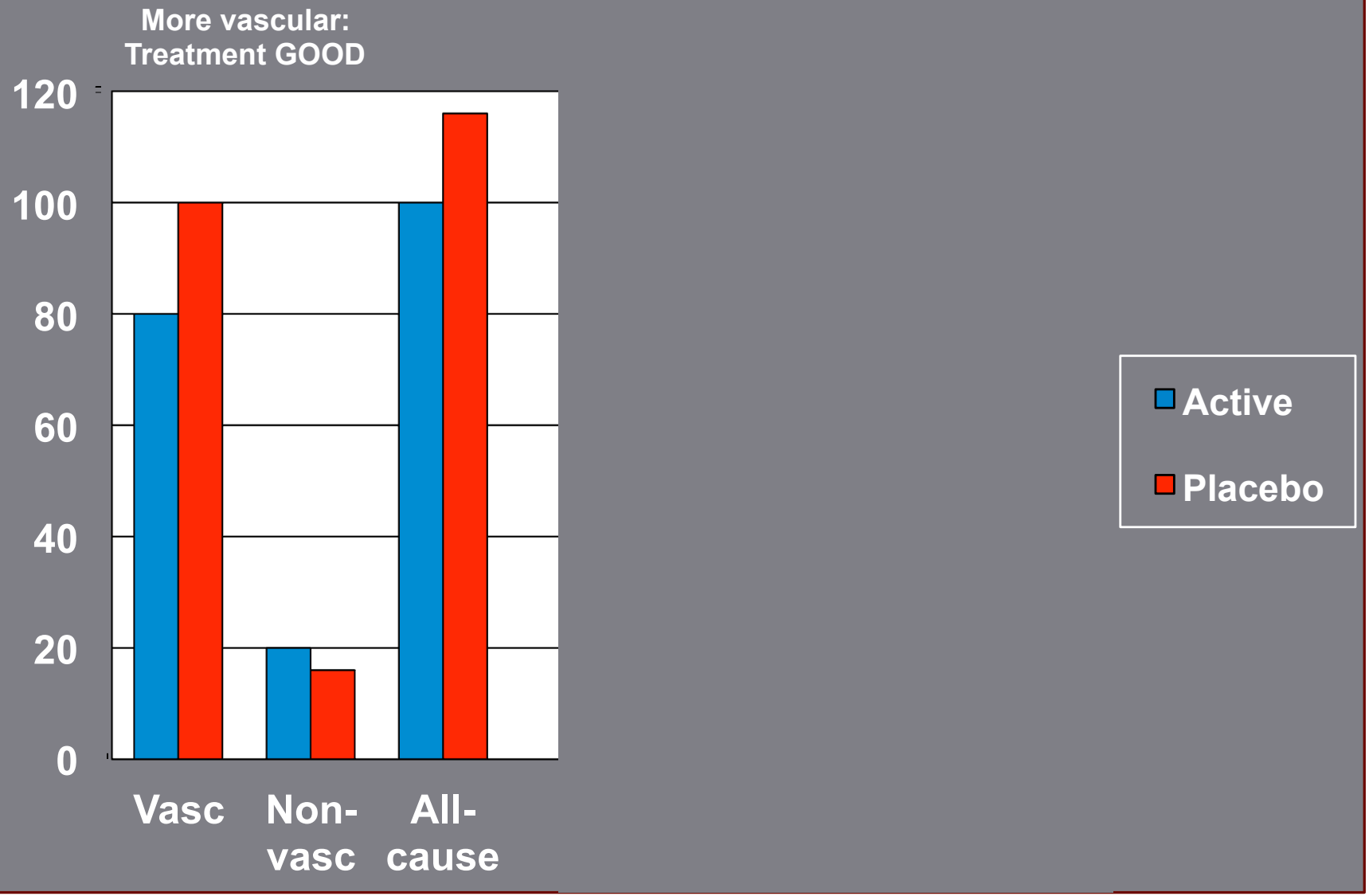
Sufficient numbers of relevant events

* Number of events, not participants, is chief determinant of power

* Composite outcomes that combine events which may involve different directions of effect are less sensitive and generalizable (e.g. total mortality, or total cancer)

* Treatment effects (hazards & benefits) may emerge at different time points

Direction of effect on all-cause mortality depends on proportions of vascular & non-vascular death



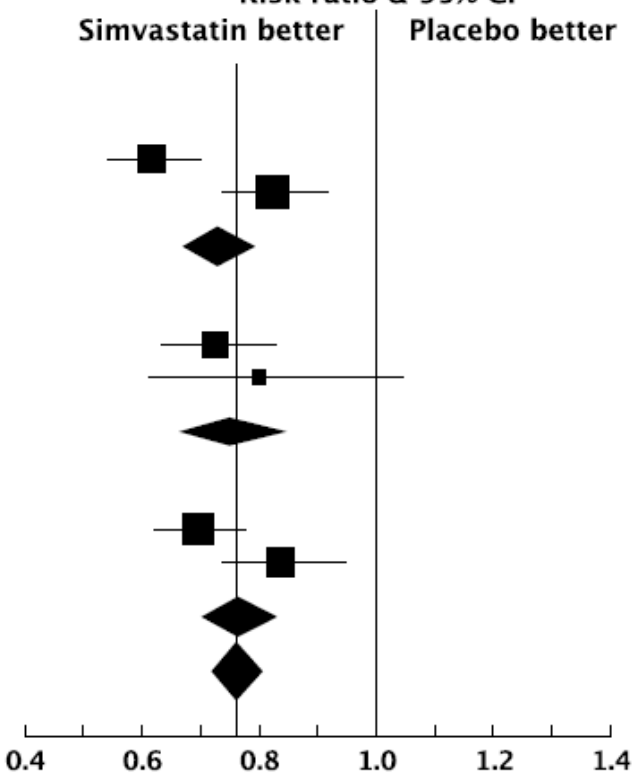
Avoid undue emphasis on data points

Reliable RESULT ≠ Accurate DATA

Accurate DATA ≠ Reliable RESULT

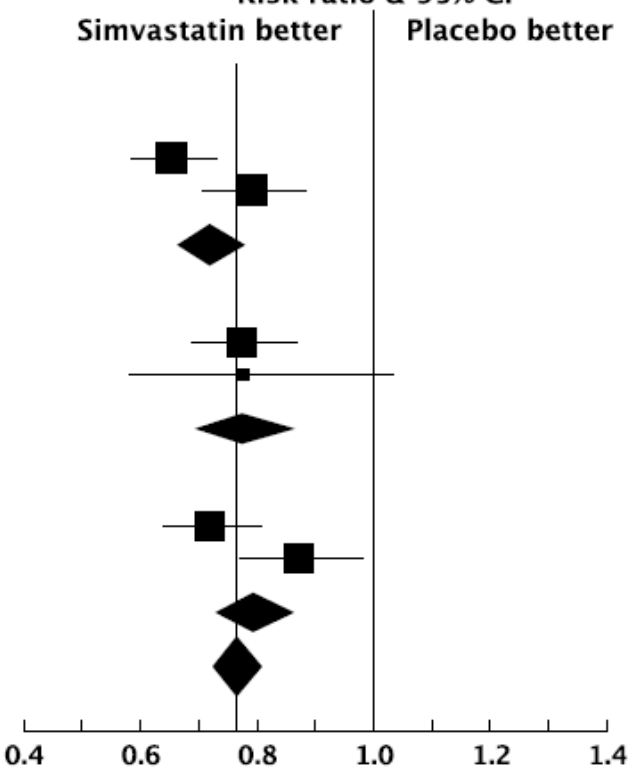
HPS: Effects of simvastatin-allocation on ADJUDICATED major vascular events

Type of event	Simvastatin allocation: Simvastatin (n=10269)		Placebo (n=10267)		Risk ratio & 95% CI
Coranary events					
Non-fatal MI	357	(3.5%)	574	(5.6%)	0.62 (0.54-0.70)
Coronary death	587	(5.7%)	707	(6.9%)	0.82 (0.74-0.92)
Any coronary event	**898**	**(8.7%)**	**1212**	**(11.8%)**	**0.73 (0.67-0.79)**
Strokes					
Non-fatal stroke	366	(3.6%)	499	(4.9%)	0.72 (0.63-0.83)
Fatal stroke	96	(0.9%)	119	(1.2%)	0.80 (0.61-1.05)
Any stroke	**444**	**(4.3%)**	**585**	**(5.7%)**	**0.75 (0.66-0.85)**
Revascularisations					
Coronary	513	(5.0%)	725	(7.1%)	0.70 (0.62-0.78)
Non-coronary	450	(4.4%)	532	(5.2%)	0.84 (0.74-0.95)
Any revascularisation	**939**	**(9.1%)**	**1205**	**(11.7%)**	**0.76 (0.70-0.83)**
ANY MAJOR VASCULAR EVENT	**2033**	**(19.8%)**	**2585**	**(25.2%)**	**0.76 (0.72-0.81)**

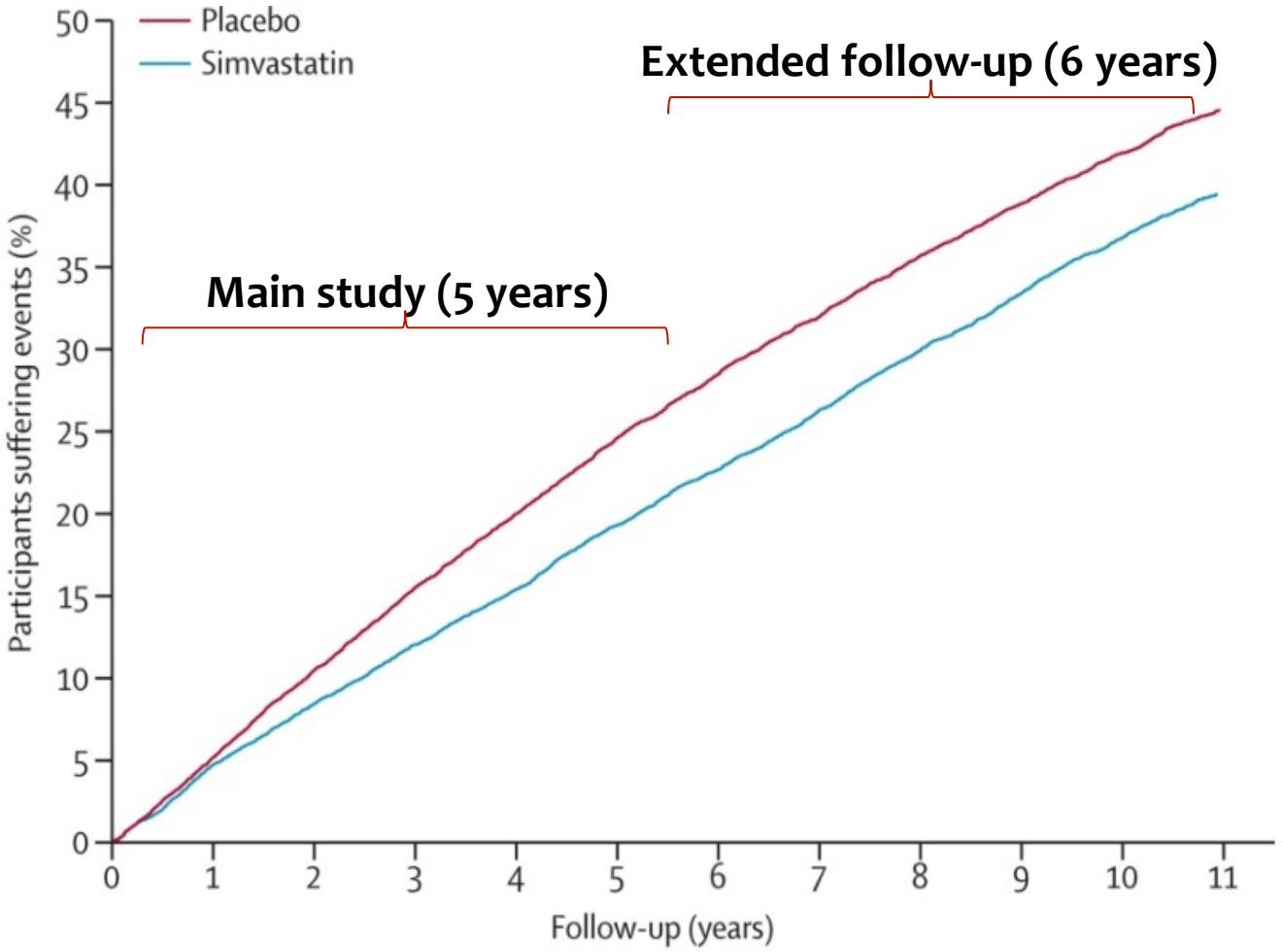


HPS: Effects of simvastatin-allocation on UNADJUDICATED major vascular events

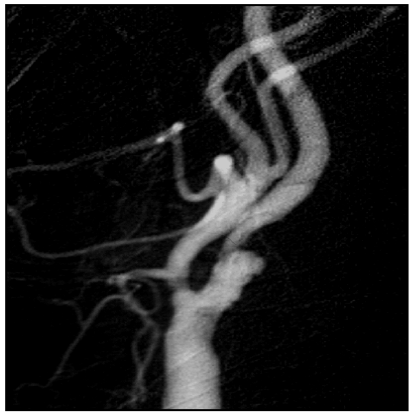
Type of event	Simvastatin allocation: Simvastatin (n=10269)		Placebo (n=10267)		Risk ratio & 95% CI
Coranary events					
Non-fatal MI	492	(4.8%)	743	(7.2%)	0.65 (0.58-0.73)
Coronary death	547	(5.3%)	687	(6.7%)	0.79 (0.71-0.88)
Any coronary event	**988**	**(9.6%)**	**1350**	**(13.1%)**	**0.72 (0.66-0.78)**
Strokes					
Non-fatal stroke	487	(4.7%)	621	(6.0%)	0.77 (0.69-0.87)
Fatal stroke	82	(0.8%)	105	(1.0%)	0.78 (0.58-1.03)
Any stroke	**550**	**(5.4%)**	**700**	**(6.8%)**	**0.77 (0.69-0.87)**
Revascularisations					
Coronary	487	(4.7%)	667	(6.5%)	0.72 (0.64-0.81)
Non-coronary	492	(4.8%)	559	(5.4%)	0.87 (0.77-0.98)
Any revascularisation	**943**	**(9.2%)**	**1166**	**(11.4%)**	**0.79 (0.73-0.86)**
ANY MAJOR VASCULAR EVENT	**2187**	**(21.3%)**	**2765**	**(26.9%)**	**0.77 (0.72-0.81)**

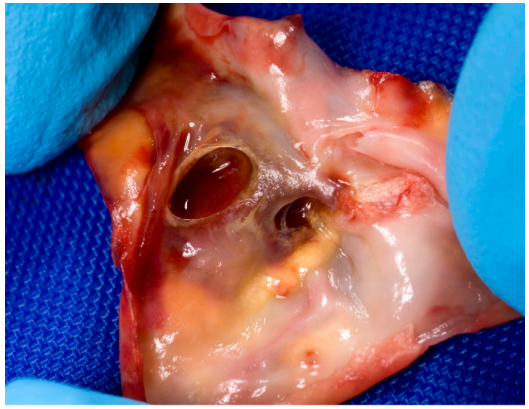


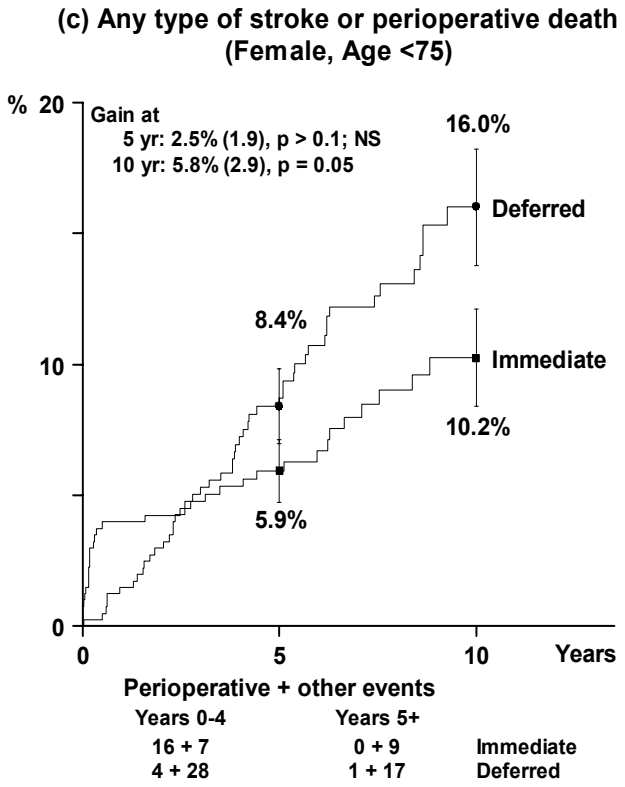
Prolonged follow-up of participants after the MRC/ BHF Heart Protection Study



Surgery for asymptomatic carotid surgery reduces 10-year risk of stroke







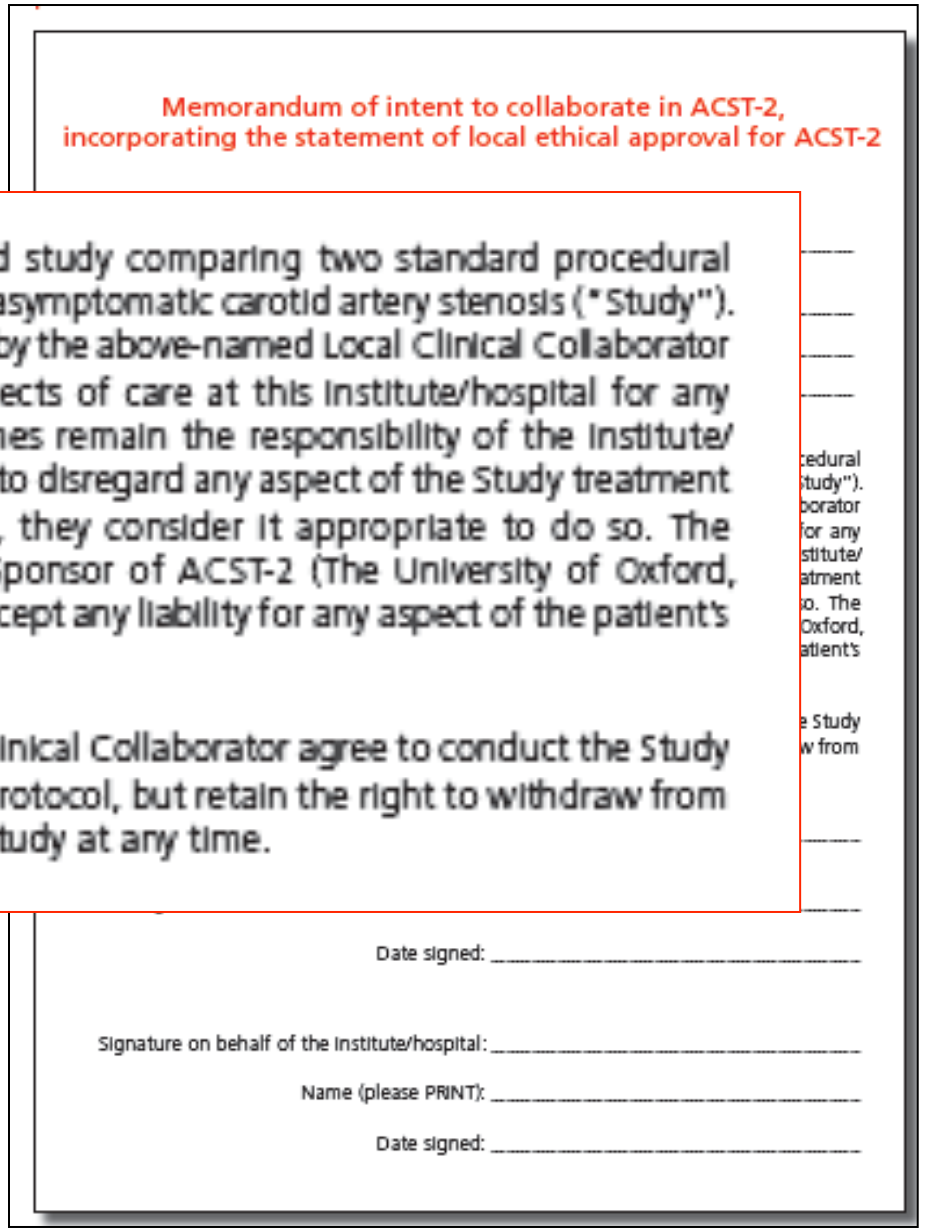
BUT: Stenting might be better:

no incision, quick discharge, no cranial nerve damage

Carotid surgery or carotid stenting? - wide variation in current practice

North America	~50% stenting	>100,000 pa (95% asymptomatic)
Europe	~40% stenting	>100,000 pa (60% asymptomatic)
United Kingdom	~10% stenting	

Large streamlined study



Memorandum of intent to collaborate in ACST-2, incorporating the statement of local ethical approval for ACST-2

ACST-2 is a long-term, large-scale randomised study comparing two standard procedural interventions for the treatment of patients with asymptomatic carotid artery stenosis ("Study"). The Study has ethics approval that was obtained by the above-named Local Clinical Collaborator at the above named institute/hospital. All aspects of care at this institute/hospital for any patient recruited into the Study shall at all times remain the responsibility of the institute/hospital and its staff. The staff retain their right to disregard any aspect of the Study treatment allocation for that patient if, in their opinion, they consider it appropriate to do so. The institute/hospital recognises that neither the Sponsor of ACST-2 (The University of Oxford, UK) nor St George's University of London, UK accept any liability for any aspect of the patient's treatment or its consequences.

The institute/hospital and above-named Local Clinical Collaborator agree to conduct the Study in accordance with the principles of the Study protocol, but retain the right to withdraw from the Study or withdraw any patients from the Study at any time.

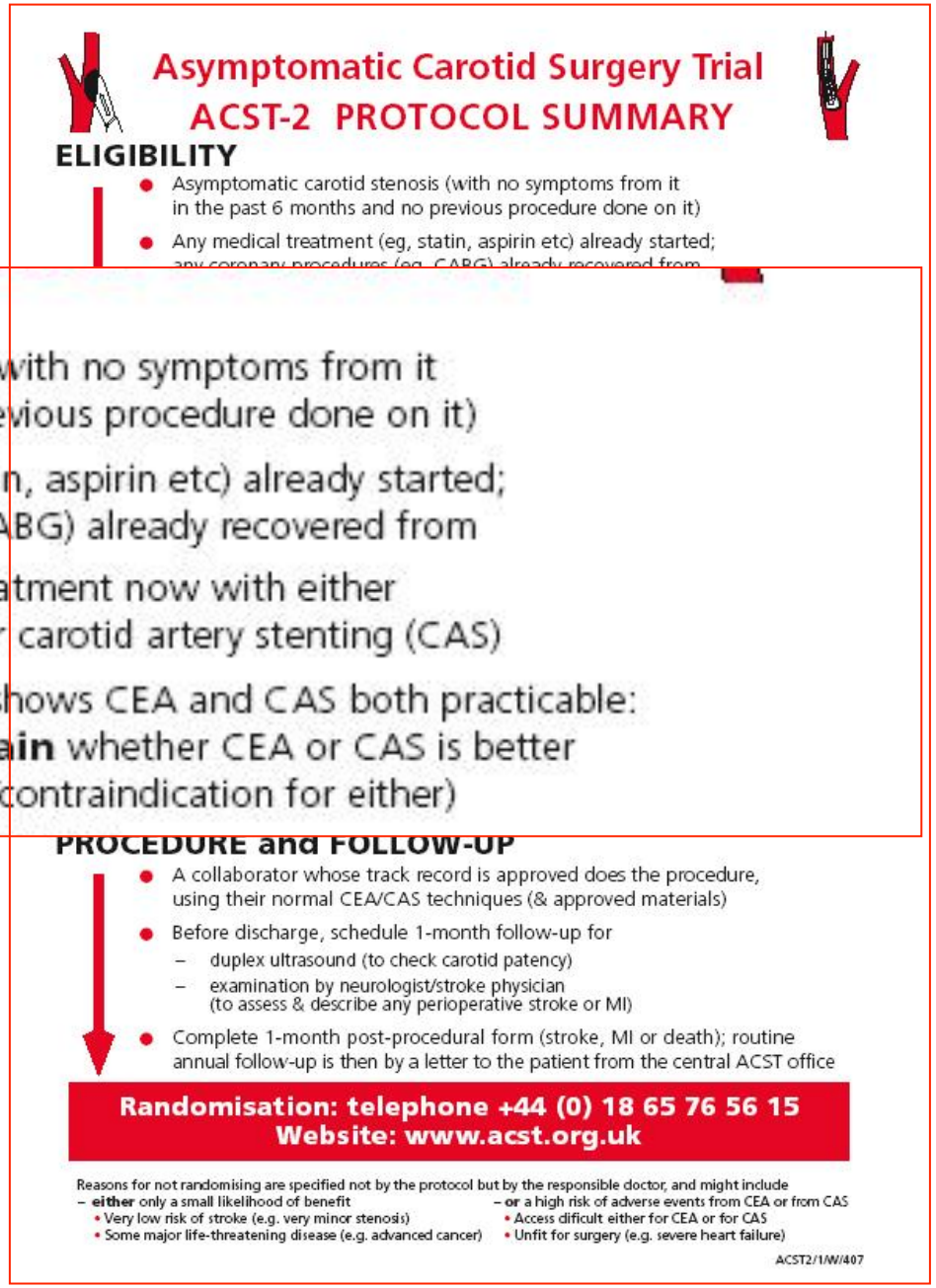
Date signed: _____

Signature on behalf of the institute/hospital: _____

Name (please PRINT): _____

Date signed: _____

Large streamlined study



ELIGIBILITY

- Asymptomatic carotid stenosis (with no symptoms from it in the past 6 months and no previous procedure done on it)
- Any medical treatment (eg, statin, aspirin etc) already started; any coronary procedures (eg, CABG) already recovered from
- Thought to need procedural treatment now with either carotid endarterectomy (CEA) or carotid artery stenting (CAS)
- MRA, CTA or other angiogram shows CEA and CAS both practicable: doctor **substantially uncertain** whether CEA or CAS is better (and sees no definite indication/contraindication for either)

Designed to fit in with routine clinical care

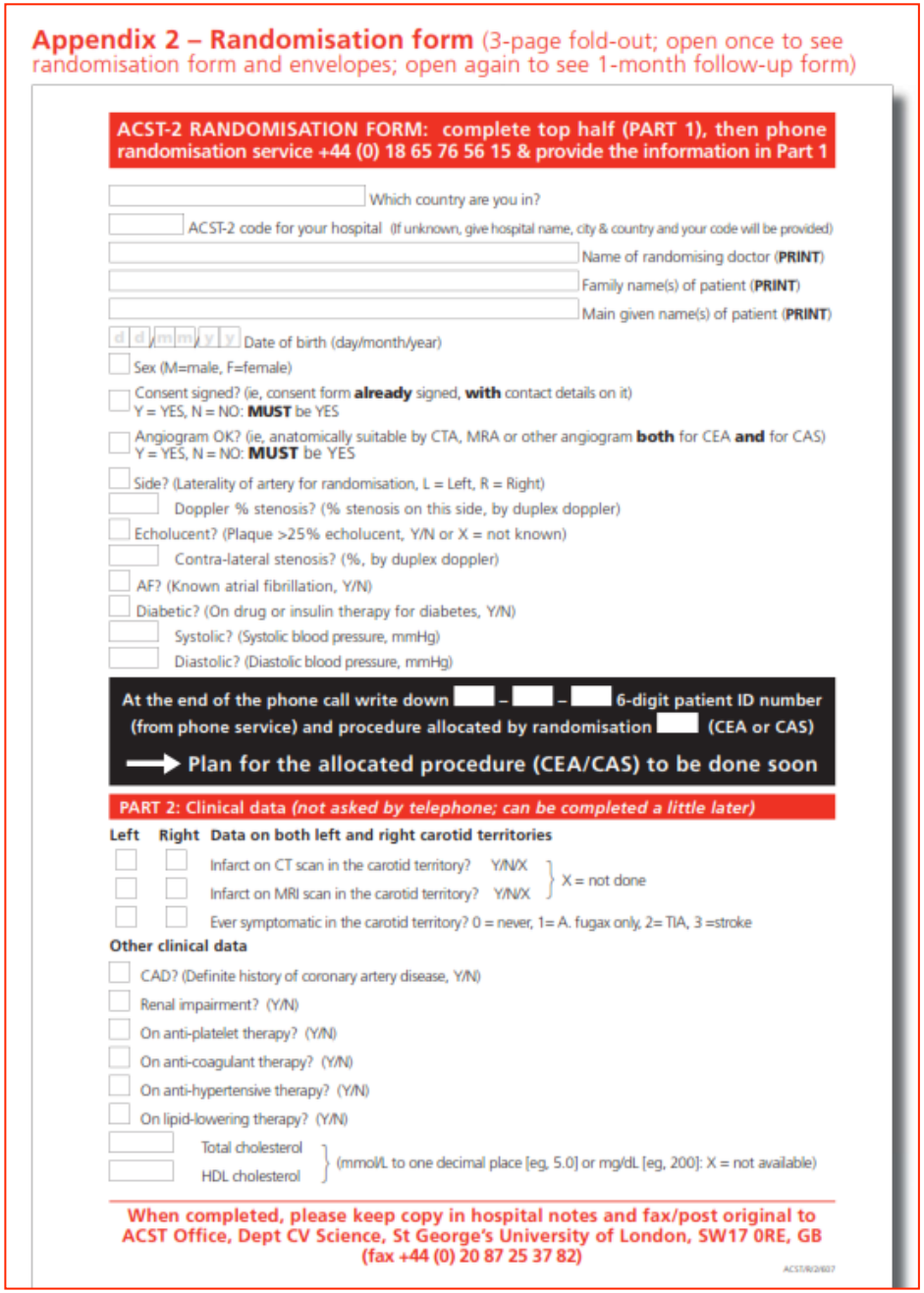
Randomisation

Single page form

Via Web / 24hr Freefone

Part 1 required for minimisation

Limited baseline data sought



Appendix 2 – Randomisation form (3-page fold-out; open once to see randomisation form and envelopes; open again to see 1-month follow-up form)

ACST-2 RANDOMISATION FORM: complete top half (PART 1), then phone randomisation service +44 (0) 18 65 76 56 15 & provide the information in Part 1

- Which country are you in?
- ACST-2 code for your hospital (If unknown, give hospital name, city & country and your code will be provided)
- Name of randomising doctor (**PRINT**)
- Family name(s) of patient (**PRINT**)
- Main given name(s) of patient (**PRINT**)
- d d / m m / y y Date of birth (day/month/year)
- Sex (M=male, F=female)
- Consent signed? (ie, consent form **already** signed, **with** contact details on it) Y = YES, N = NO: **MUST** be YES
- Angiogram OK? (ie, anatomically suitable by CTA, MRA or other angiogram **both** for CEA **and** for CAS) Y = YES, N = NO: **MUST** be YES
- Side? (Laterality of artery for randomisation, L = Left, R = Right)
- Doppler % stenosis? (% stenosis on this side, by duplex doppler)
- Echolucent? (Plaque >25% echolucent, Y/N or X = not known)
- Contra-lateral stenosis? (%, by duplex doppler)
- AF? (Known atrial fibrillation, Y/N)
- Diabetic? (On drug or insulin therapy for diabetes, Y/N)
- Systolic? (Systolic blood pressure, mmHg)
- Diastolic? (Diastolic blood pressure, mmHg)

At the end of the phone call write down ___ – ___ – ___ 6-digit patient ID number (from phone service) and procedure allocated by randomisation ___ (CEA or CAS)

→ Plan for the allocated procedure (CEA/CAS) to be done soon

PART 2: Clinical data ***(not asked by telephone; can be completed a little later)***

Left Right Data on both left and right carotid territories

- Infarct on CT scan in the carotid territory? Y/N/X
- Infarct on MRI scan in the carotid territory? Y/N/X

} X = not done

- Ever symptomatic in the carotid territory? 0 = never, 1= A. fugax only, 2= TIA, 3 =stroke

Other clinical data

- CAD? (Definite history of coronary artery disease, Y/N)
- Renal impairment? (Y/N)
- On anti-platelet therapy? (Y/N)
- On anti-coagulant therapy? (Y/N)
- On anti-hypertensive therapy? (Y/N)
- On lipid-lowering therapy? (Y/N)
- Total cholesterol
- HDL cholesterol

} (mmol/L to one decimal place [eg, 5.0] or mg/dL [eg, 200]: X = not available)

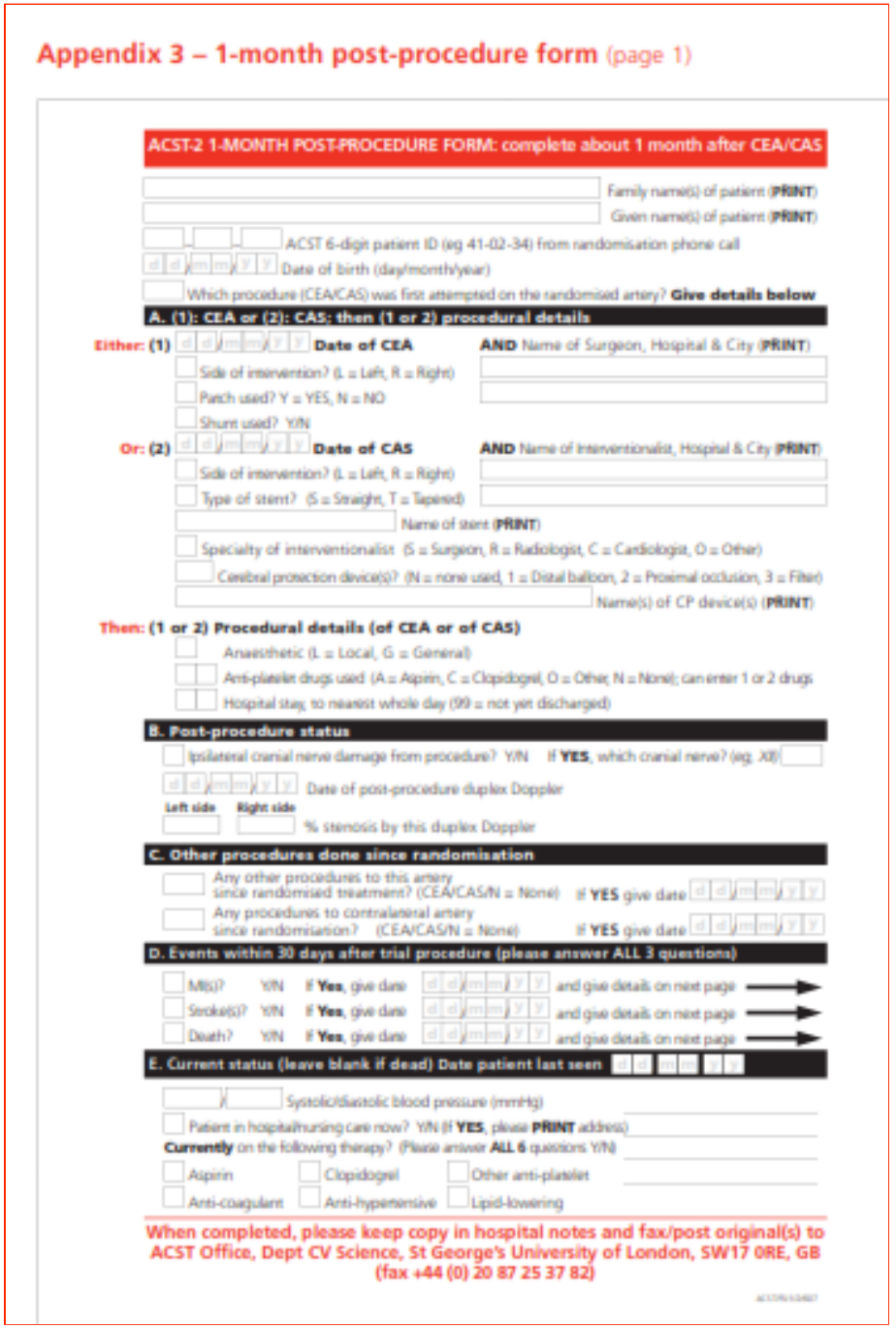
When completed, please keep copy in hospital notes and fax/post original to ACST Office, Dept CV Science, St George's University of London, SW17 0RE, GB (fax +44 (0) 20 87 25 37 82)

ACST/R/2/607

1-month Follow-up

- Single page form
- Procedural details
- Post-procedure status
  - Residual stenosis
  - Cranial nerve damage
  - MI*
  - Stroke*
  - Death* (* *further details provided)*
  - BP
  - Adjunctive medical therapy

No more work for collaborators



Appendix 3 – 1-month post-procedure form (page 1)

ACST-2 1-MONTH POST-PROCEDURE FORM: complete about 1 month after CEA/CAS

Family name(s) of patient (PRINT)

Given name(s) of patient (PRINT)

ACST 6-digit patient ID (eg 41-02-34) from randomisation phone call

Date of birth (day/month/year)

Which procedure (CEA/CAS) was first attempted on the randomised artery? **Give details below**

A. (1): CEA or (2): CAS; then (1 or 2) procedural details

Either: (1) Date of CEA — **AND** Name of Surgeon, Hospital & City (PRINT)

Side of intervention? (L = Left, R = Right)

Patch used? Y = YES, N = NO

Shunt used? Y/N

Or: (2) Date of CAS — **AND** Name of Interventionalist, Hospital & City (PRINT)

Side of intervention? (L = Left, R = Right)

Type of stent? (S = Straight, T = Tapered)

Name of stent (PRINT)

Specialty of interventionalist (S = Surgeon, R = Radiologist, C = Cardiologist, O = Other)

Cerebral protection device(s)? (N = none used, 1 = Distal balloon, 2 = Proximal occlusion, 3 = Filter)

Name(s) of CP device(s) (PRINT)

Then: (1 or 2) Procedural details (of CEA or of CAS)

Anaesthetic (L = Local, G = General)

Anti-platelet drugs used (A = Aspirin, C = Clopidogrel, O = Other, N = None); can enter 1 or 2 drugs

Hospital stay, to nearest whole day (99 = not yet discharged)

B. Post-procedure status

Ipsilateral cranial nerve damage from procedure? Y/N — If **YES**, which cranial nerve? (eg. XII)

Date of post-procedure duplex Doppler

Left side / Right side — % stenosis by this duplex Doppler

C. Other procedures done since randomisation

Any other procedures to this artery since randomised treatment? (CEA/CAS/N = None) — If **YES** give date

Any procedures to contralateral artery since randomisation? (CEA/CAS/N = None) — If **YES** give date

D. Events within 30 days after trial procedure (please answer ALL 3 questions)

MI(s)? Y/N — If **Yes**, give date — and give details on next page →

Stroke(s)? Y/N — If **Yes**, give date — and give details on next page →

Death? Y/N — If **Yes**, give date — and give details on next page →

E. Current status (leave blank if dead) Date patient last seen

/ Systolic/diastolic blood pressure (mmHg)

Patient in hospital/nursing care now? Y/N (If **YES**, please **PRINT** address)

Currently on the following therapy? (Please answer **ALL 6** questions Y/N)

Aspirin — Clopidogrel — Other anti-platelet

Anti-coagulant — Anti-hypertensive — Lipid-lowering

When completed, please keep copy in hospital notes and fax/post original(s) to ACST Office, Dept CV Science, St George's University of London, SW17 0RE, GB (fax +44 (0) 20 87 25 37 82)

Annual Follow-up by postal questionnaire

Completed by patient or alternative contact

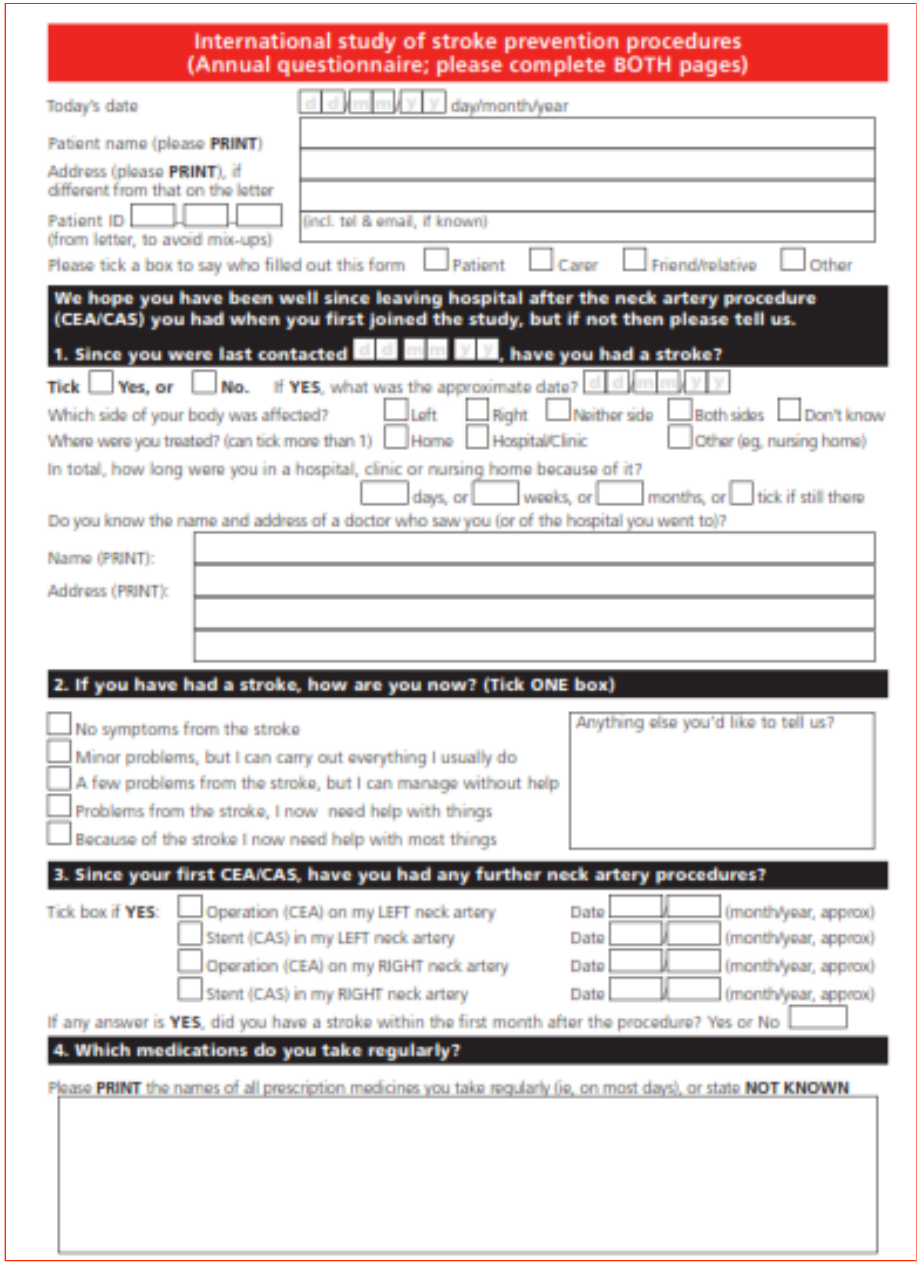
Questions:

Stroke?

Severity?

Any carotid procedures?

Medications



International study of stroke prevention procedures
(Annual questionnaire; please complete BOTH pages)

Today's date d d m m y y day/month/year

Patient name (please **PRINT**)

Address (please **PRINT**), if different from that on the letter

Patient ID (from letter, to avoid mix-ups)

(incl. tel & email, if known)

Please tick a box to say who filled out this form ☐ Patient ☐ Carer ☐ Friend/relative ☐ Other

We hope you have been well since leaving hospital after the neck artery procedure (CEA/CAS) you had when you first joined the study, but if not then please tell us.

1. Since you were last contacted d d m m y y, have you had a stroke?

Tick ☐ **Yes, or** ☐ **No.** If **YES**, what was the approximate date? d d m m y y

Which side of your body was affected? ☐ Left ☐ Right ☐ Neither side ☐ Both sides ☐ Don't know

Where were you treated? (can tick more than 1) ☐ Home ☐ Hospital/Clinic ☐ Other (eg, nursing home)

In total, how long were you in a hospital, clinic or nursing home because of it?

☐ days, or ☐ weeks, or ☐ months, or ☐ tick if still there

Do you know the name and address of a doctor who saw you (or of the hospital you went to)?

Name (PRINT):

Address (PRINT):

2. If you have had a stroke, how are you now? (Tick ONE box)

☐ No symptoms from the stroke
☐ Minor problems, but I can carry out everything I usually do
☐ A few problems from the stroke, but I can manage without help
☐ Problems from the stroke, I now need help with things
☐ Because of the stroke I now need help with most things

Anything else you'd like to tell us?

3. Since your first CEA/CAS, have you had any further neck artery procedures?

Tick box if **YES**:

☐ Operation (CEA) on my LEFT neck artery — Date / (month/year, approx)
☐ Stent (CAS) in my LEFT neck artery — Date / (month/year, approx)
☐ Operation (CEA) on my RIGHT neck artery — Date / (month/year, approx)
☐ Stent (CAS) in my RIGHT neck artery — Date / (month/year, approx)

If any answer is **YES**, did you have a stroke within the first month after the procedure? Yes or No

4. Which medications do you take regularly?

Please **PRINT** the names of all prescription medicines you take regularly (ie, on most days), or state **NOT KNOWN**

Efficient use of resources

ACST-1 and ACST-2 cost <u>one-tenth</u> of the corresponding North American trials, but recruited <u>double</u> the number of patients

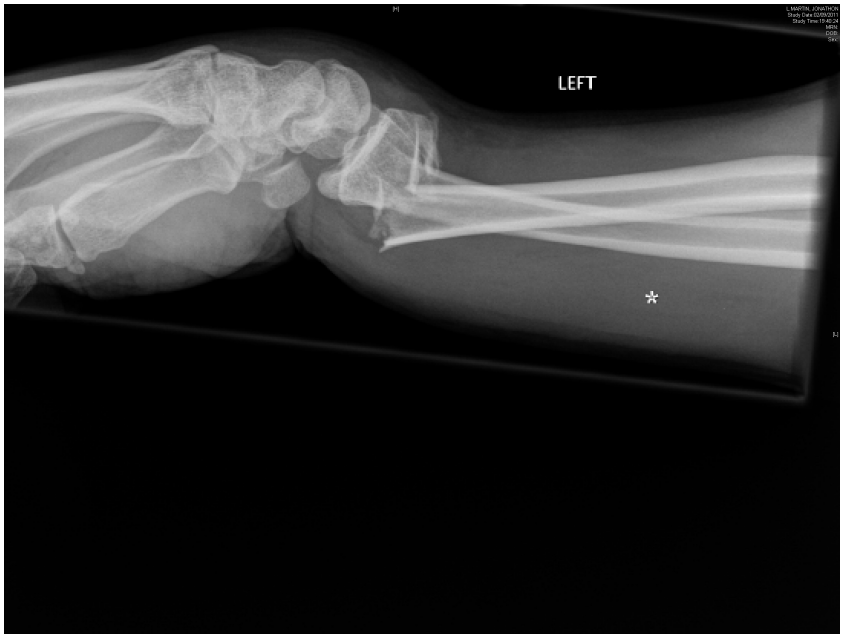
ACAS – US $24m
(1700 patients)

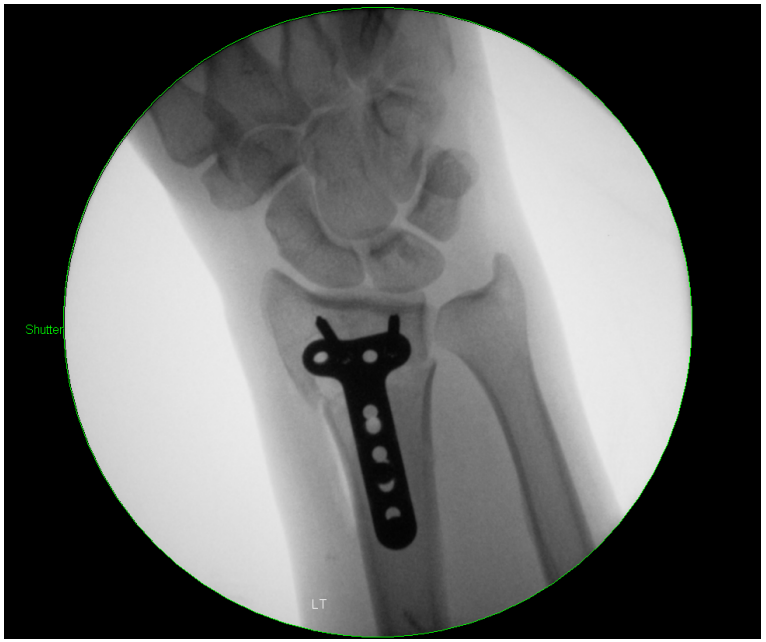
CREST-1 – US $80m
(2500 patients,
half asymptomatic)

ACST-1 – £1.2m
(3100 patients)

ACST-2 –~£4m by 2019
(3000-4000 patients)

Distal Radius Acute Fracture Fixation Trial (ISRCTN 31379280)





Inclusion criterion:	Dorsally displaced fracture of distal radius
Randomized intervention:	Percutaneous fixation with Kirschner wires vs. Volar locking plate
Primary outcome:	Patient Related Wrist Evaluation at one year
Recruitment:	Target: 390. Achieved: 461

What's the patient perspective?

* What do the 2 alternative interventions involve?
  * is there really uncertainty about how to treat this?
  * how quickly will I be able to work (type, drive, fly)?
  * what about long-term function (e.g. piano, cello, arthritis)
  * if I am randomized to one intervention, will I regret that I didn't get the other?
* How much effort will this be for me?
  * e.g. visits, forms, X-rays
* Is the trial likely to provide a useful answer?
  * is it focussing on an important outcome?
  * is it sufficiently large? how is recruitment going?

Summary

* Objective: Improve the availability of reliable information on for important healthcare decisions
* Design quality in to the trial protocol and procedures
* Identify and address risks as trial progresses
* Focus efforts to enhance quality (including monitoring):
  * Appropriate to the setting
  * Proportionate to the risks
  * Foster improvement
* Be open about quality assurance
  * Share management plans and issues identified