Quality Risk Assessment and Quality by Design in Clinical Research

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“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)

Protocol (Plan)
- assess key risks (likelihood, impact)
- plan mitigation
- plan evaluation

Operations (Do)
- organization, training, systems and procedures tailored to the protocol

Monitoring (Check)
- measure and evaluate performance

Make improvements (Act)
- re-assess risks
- make appropriate changes to protocol, operations or monitoring

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.

More vascular: Treatment GOOD

More non-vascular:

Treatment BAD
Avoid undue emphasis on data points

Reliable RESULT ≠ Accurate DATA

Accurate DATA ≠ Reliable RESULT
HPS: Effects of simvastatin-allocation on ADJUDICATED major vascular events

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

Risk ratios and 95% confidence intervals indicate a statistically significant reduction in major vascular events with simvastatin compared to placebo.
HPS: Effects of simvastatin-allocation on UNADJUDICATED major vascular events

| Type of event                | Simvastatin allocation | Placebo allocation | Risk ratio & 95% CI
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<td>Coro onary events</td>
<td></td>
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<td></td>
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<tr>
<td>Non-fatal MI</td>
<td>492 (4.8%)</td>
<td>743 (7.2%)</td>
<td>0.65 (0.58-0.73)</td>
</tr>
<tr>
<td>Coronary death</td>
<td>547 (5.3%)</td>
<td>687 (6.7%)</td>
<td>0.79 (0.71-0.88)</td>
</tr>
<tr>
<td>Any coronary event</td>
<td>988 (9.6%)</td>
<td>1350 (13.1%)</td>
<td>0.72 (0.66-0.78)</td>
</tr>
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<tr>
<td>Non-fatal stroke</td>
<td>487 (4.7%)</td>
<td>621 (6.0%)</td>
<td>0.77 (0.69-0.87)</td>
</tr>
<tr>
<td>Fatal stroke</td>
<td>82 (0.8%)</td>
<td>105 (1.0%)</td>
<td>0.78 (0.58-1.03)</td>
</tr>
<tr>
<td>Any stroke</td>
<td>550 (5.4%)</td>
<td>700 (6.8%)</td>
<td>0.77 (0.69-0.87)</td>
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<tr>
<td>Any revascularisation</td>
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<td>1166 (11.4%)</td>
<td>0.79 (0.73-0.86)</td>
</tr>
<tr>
<td>ANY MAJOR VASCULAR EVENT</td>
<td>2187 (21.3%)</td>
<td>2765 (26.9%)</td>
<td>0.77 (0.72-0.81)</td>
</tr>
</tbody>
</table>
Prolonged follow-up of participants after the MRC/BHF Heart Protection Study

Extended follow-up (6 years)

Main study (5 years)
Surgery for asymptomatic carotid surgery reduces 10-year risk of stroke

(c) Any type of stroke or perioperative death (Female, Age <75)

% Gain at
5 yr: 2.5% (1.9), p > 0.1; NS
10 yr: 5.8% (2.9), p = 0.05

Deferred
10.2%

Immediate
8.4%

5.9%

Deferred

Years 0-4
16 + 7
4 + 28

Years 5+
0 + 9
1 + 17

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
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: __________________________
**ELIGIBILITY**

- Asymptomatic carotid stenosis (with no symptoms from it in the past 6 months and no previous procedure done on it)
- Any medical treatment (e.g., statin, aspirin etc) already started; any coronary procedures (e.g., 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)

**PROCEDURE AND FOLLOW-UP**

- A collaborator whose track record is approved does the procedure, using their normal CEA/CAS techniques (& approved materials)
- Before discharge, schedule 1-month follow-up for
  - duplex ultrasound (to check carotid patency)
  - examination by neurologist/stroke physician (to assess & describe any perioperative stroke or MI)
- Complete 1-month post-procedural form (stroke, MI or death); routine annual follow-up is then by a letter to the patient from the central ACST office

**Randomisation:** telephone +44 (0) 18 65 76 56 15
**Website:** www.acst.org.uk

Reasons for not randomising are specified not by the protocol but by the responsible doctor, and might include
- either only a small likelihood of benefit
- very low risk of stroke (e.g., very minor stenosis)
- access difficult either for CEA or for CAS
- or a high risk of adverse events from CEA or from CAS
- or a high risk of adverse events from CEA or from CAS
- unfitness for surgery (e.g., severe heart failure)

**Maximise recruitment by minimizing collaborator’s workload**

**Large streamlined study**

**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
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
Annual Follow-up by postal questionnaire

Completed by patient or alternative contact

Questions:
1. Stroke?
2. Severity?
3. Any carotid procedures?
4. Medications
Efficient use of resources

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

<table>
<thead>
<tr>
<th>Trial</th>
<th>Funding</th>
<th>Patients (Asymptomatic)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACAS</td>
<td>US $24m</td>
<td>(1700 patients)</td>
</tr>
<tr>
<td>CREST-1</td>
<td>US $80m</td>
<td>(2500 patients, half asymptomatic)</td>
</tr>
<tr>
<td>ACST-1</td>
<td>£1.2m</td>
<td>(3100 patients)</td>
</tr>
<tr>
<td>ACST-2</td>
<td>~£4m by 2019</td>
<td>(3000-4000 patients)</td>
</tr>
</tbody>
</table>
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?
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