What are the key drivers for quality?

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University of Oxford
Need for reliable evidence from clinical trials

* Essential for appropriate decision making concerning the benefits and risks associated with clinical interventions.

* Decisions made in the absence of reliable evidence (either because relevant trials have never been performed or because those that have been performed were poorly designed or conducted) may harm individual patients and public health.
Criteria for a good trial

* Ask an IMPORTANT question
* Answer it RELIABLY
“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

* 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
Facilitating recruitment

* Protocol
  * Inclusion criteria
    * relevant to target population
    * at sufficient risk of the key outcomes
    * differentiate from participant characterization
  * Exclusion criteria
    * human subjects protection
      * focus on comorbidity, concomitant medication, consent
      * avoid unnecessary criteria (if you don’t study it, you’ll never know)

* Operations
  * Site selection
  * Pre-screening
• Pre-screening to identify potentially eligible individuals
• Use of electronic data records (where available)

<table>
<thead>
<tr>
<th>Description</th>
<th>Count</th>
</tr>
</thead>
<tbody>
<tr>
<td>UK Sites</td>
<td>88</td>
</tr>
<tr>
<td>Identify</td>
<td>300,000</td>
</tr>
<tr>
<td>Invite</td>
<td>230,000</td>
</tr>
<tr>
<td>Screen</td>
<td>24,000  (10%)</td>
</tr>
<tr>
<td>Consent</td>
<td>16,000  (7%)</td>
</tr>
<tr>
<td>Randomized</td>
<td>8,000   (3%)</td>
</tr>
<tr>
<td>(per site)</td>
<td>~90</td>
</tr>
</tbody>
</table>
Value of pre-screening

Complete Enrolment (7000 participants):
Projected: 15 months
Value of pre-screening

Complete Enrolment (7000 participants):
Projected: 15 months
Actual: 7 months

- Number successfully screened
- Projected vs Actual
- Months from Sep to Dec
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
Unbiased treatment allocation & follow-up

* No foreknowledge of likely treatment allocation
* Meaningful treatment difference
* Minimize post-randomisation withdrawals (i.e. intent-to-treat)
* Minimize losses to follow-up (e.g. after primary event occurs or study treatment stops)
Focus on what matters: Randomization
Biased (i.e. non-randomized) follow-up & analysis

<table>
<thead>
<tr>
<th></th>
<th>Active</th>
<th>Placebo</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Randomized</td>
<td>6481</td>
<td>6536</td>
<td></td>
</tr>
<tr>
<td>Not willing/ineligible</td>
<td>117</td>
<td>159</td>
<td>=0.02</td>
</tr>
<tr>
<td>Received treatment</td>
<td>6364</td>
<td>6377</td>
<td></td>
</tr>
<tr>
<td>Withdrew consent</td>
<td>343</td>
<td>396</td>
<td>=0.05</td>
</tr>
<tr>
<td>Lost to follow-up</td>
<td>367</td>
<td>369</td>
<td>&gt;0.05</td>
</tr>
</tbody>
</table>

Comparison of the 6364 versus 6377 who received treatment described as having been “Analyzed by intention-to-treat”
### Impact of non-compliance

<table>
<thead>
<tr>
<th>Treatment effect on biomarker</th>
<th>Anticipated relative risk reduction</th>
<th>Active (n=4000)</th>
<th>Control (n=4000)</th>
<th>Power at p=0.01</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.0</td>
<td>20%</td>
<td>480 (12.0%)</td>
<td>600 (15.0%)</td>
<td>91%</td>
</tr>
</tbody>
</table>

Not to check these assumptions may have adverse public health implications
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><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>
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# HPS: Effects of simvastatin-allocation on UNADJUDICATED major vascular events

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</tr>
</thead>
<tbody>
<tr>
<td><strong>Coronary events</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<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><strong>Any coronary event</strong></td>
<td>988 (9.6%)</td>
<td>1350 (13.1%)</td>
<td>0.72 (0.66-0.78)</td>
</tr>
<tr>
<td><strong>Strokes</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<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><strong>Any stroke</strong></td>
<td>550 (5.4%)</td>
<td>700 (6.8%)</td>
<td>0.77 (0.69-0.87)</td>
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<td><strong>Any revascularisation</strong></td>
<td>943 (9.2%)</td>
<td>1166 (11.4%)</td>
<td>0.79 (0.73-0.86)</td>
</tr>
<tr>
<td><strong>ANY MAJOR VASCULAR EVENT</strong></td>
<td>2187 (21.3%)</td>
<td>2765 (26.9%)</td>
<td>0.77 (0.72-0.81)</td>
</tr>
</tbody>
</table>
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
Conclusions

* 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