An introduction to Quality by Design

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University of Oxford
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
  * 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
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 stops active treatment
  * Active group starts other treatment (e.g. effective comparator)
  * Control group starts active treatment (unusual in IND studies)

* Impact on results
  * less difference between randomized groups
  * conservative for superiority assessments
  * counter-conservative for non-inferiority / safety assessments
## 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
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
Size of effect on all-cause mortality depends on proportions of infection & other deaths

More infection: Treatment CLEARLY GOOD

More non-infection: Treatment MODEST

Size of effect on all-cause mortality depends on proportions of infection & other deaths

Active

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

- Placebo
- Simvastatin

Extended follow-up (6 years)

Main study (5 years)
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 (n=10269)</th>
<th>Placebo (n=10267)</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>
</tbody>
</table>
HPS: Effects of simvastatin-allocation on UNADJUDICATED 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>Simvastatin better</td>
</tr>
<tr>
<td>Coro nary events</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>Any coronary event</td>
<td>988 (9.6%)</td>
<td>1350 (13.1%)</td>
<td>0.72 (0.66-0.78)</td>
</tr>
<tr>
<td>Strokes</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 (0.73-0.98)</td>
</tr>
<tr>
<td>Any stroke</td>
<td>550 (5.4%)</td>
<td>700 (6.8%)</td>
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</tr>
<tr>
<td>Any revascularisation</td>
<td>943 (9.2%)</td>
<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>
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
Some examples from cardiovascular field
ISIS2: Design

Population: Acute myocardial infarction
Sample size: 17,187
Intervention: Streptokinase vs. placebo
Aspirin vs. placebo
Compliance: Not recorded
Follow-up: 5 weeks
Primary outcome: Vascular mortality
Year of completion: 1988
“By far the most important determinant of the success of ISIS is the extent to which, in those busy hospitals where the majority of acute MI patients are actually admitted, the responsible physicians and nurses choose to enter their patients. Hence, the extra work must be – and is – absolutely minimal.”
Eligibility

- Signs or symptoms suggestive of definite or suspected acute myocardial infarction
- <24 hours since onset of episode of pain that led to admission
- No clear contra-indication to, or indication for, immediate streptokinase or aspirin, in the view of the responsible physician

Randomization

- By telephone - 9 questions plus site and patient identifiers

Follow-up data collection

- Discharge form
- Pre-randomization ECG
### PATIENT IDENTIFIERS

Please PRINT:
(for central monitoring of certified causes of death)

- **Hospital:**
- **Surname/Family name:**
- **All given names:**
- **Date of birth:** day, month, year:
- **Address:**

- **Maine name:**
- **Family doctor:**

### PRE-TREATMENT CHARACTERISTICS

- **Female:**
- **Previous myocardial infarction:**
- **Previous diabetes:**

### ANY DEVIATIONS FROM TRIAL TREATMENT

- **STREPTOKINASE/PLACEBO infusion interrupted, or not given:**
- **ASPIRIN/PLACEBO calendar pack interrupted, or not given:**

### APPARENT SIDE-EFFECTS OF STREPTOKINASE/PLACEBO INFUSION

- **Significant hypotension during, or just after, infusion:**
- **Anaphylactic shock:**
- **Rash:**
- **Other:**

### MAIN EVENTS (FATAL OR NOT) AFTER RANDOMISATION, AND ENTER DATE (FIRST) OCCURRED

- **“Major” bleed (transferred):**
- **“Minor” bleed (not transfused):**
- **Cardiac rupture:**
- **Myocardial infarction:**
- **Ventricular fibrillation:**
- **Other cardiac arrest:**
- **Stroke, probable cerebral haemorrhage:**
- **Stroke, intact or unknown type:**
- **Discharge alive from hospital:**
- **Deaths in hospital:**

### TREATMENT IN HOSPITAL

- **Steroids prior to streptokinase/placebo infusion:**
- **Subcutaneous heparin:**
- **Intravenous heparin:**
- **Ox and/or placebo:**
- **Intravenous beta-blocker:**
- **Non-trial aspirin:**
- **Other anti-platelet agents:**

### DRUGS ON DISCHARGE

- **Oral anticoagulant:**
- **Non-trial aspirin:**
- **Other anti-platelet agents:**
- **Beta-blocker:**

### NAME OF PERSON COMPLETING FORM

- **[Print]:**

Please send: — TOP COPY OF THIS FORM (retain bottom green copy) — AND PRE-RANDOMISATION ECC (original or good photocopy)

TO: ISIS-2, FREEPOST, OXFORD OX2 6RR, UK (no stamp required within UK)
Second International Study of Infarct Survival (ISIS-2)

Routine Care
13% dead

Aspirin only

Streptokinase only

Routine care + Streptokinase and Aspirin
8% dead

Percentage dead

Weeks from starting treatment

ISIS-2 Lancet 1988
Moderate effects can influence medical practice

<table>
<thead>
<tr>
<th>Treatment</th>
<th>1987</th>
<th>1989</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antiplatelet</td>
<td>9%</td>
<td>84%</td>
</tr>
<tr>
<td>Fibrinolytics</td>
<td>2%</td>
<td>68%</td>
</tr>
<tr>
<td>Beta-blockers (oral)</td>
<td>25%</td>
<td>31%</td>
</tr>
<tr>
<td>Nitrates (oral)</td>
<td>23%</td>
<td>27%</td>
</tr>
</tbody>
</table>

BHF survey of physician treatment policies for acute MI (n=982)
Impact of large-scale randomized trials on sales of streptokinase in England & Wales

Numbers treated in each quarter

- GISSI published
- ISIS-2 interim report
- ISIS-2 report
- ISIS-2 published

<table>
<thead>
<tr>
<th>Year</th>
<th>1st quarter</th>
<th>2nd quarter</th>
<th>3rd quarter</th>
<th>4th quarter</th>
</tr>
</thead>
<tbody>
<tr>
<td>1986</td>
<td>2000</td>
<td>1000</td>
<td>500</td>
<td>1000</td>
</tr>
<tr>
<td>1987</td>
<td>4000</td>
<td>2000</td>
<td>1000</td>
<td>3000</td>
</tr>
<tr>
<td>1988</td>
<td>6000</td>
<td>3000</td>
<td>2000</td>
<td>4000</td>
</tr>
<tr>
<td>1989</td>
<td>14000</td>
<td>6000</td>
<td>4000</td>
<td>16000</td>
</tr>
</tbody>
</table>
A large, streamlined trial to assess reliably the clinical effects of lowering LDL-cholesterol among patients with chronic kidney disease
### SHARP: Design

<table>
<thead>
<tr>
<th><strong>Population</strong></th>
<th>Chronic kidney disease</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Sample size</strong></td>
<td>9,536</td>
</tr>
<tr>
<td><strong>Intervention</strong></td>
<td>Ezetimibe/simvastatin vs. placebo</td>
</tr>
<tr>
<td><strong>Compliance</strong></td>
<td>62% average net compliance</td>
</tr>
<tr>
<td></td>
<td>33 mg/dL ↓ LDL-C</td>
</tr>
<tr>
<td><strong>Follow-up</strong></td>
<td>Median 4.9 years</td>
</tr>
<tr>
<td><strong>Primary outcome</strong></td>
<td>Major atherosclerotic event</td>
</tr>
<tr>
<td><strong>Year of completion</strong></td>
<td>2010</td>
</tr>
</tbody>
</table>
SHARP: Special features of design

• Largest randomized trial in kidney patients
• Non-restrictive inclusion criteria yield widely generalizable results for CKD populations
• Included CKD patients in stages 3-5 (both pre-dialysis and dialysis)
• Focus on outcomes that are sensitive to LDL lowering (ie, major atherosclerotic events)
• Combination of moderate-dose statin plus ezetimibe yielded large LDL-C reduction, but it was also well-tolerated by CKD patients
SHARP: Wide inclusion criteria

• History of chronic kidney disease (CKD)
  – Not on dialysis: elevated creatinine on 2 occasions
    • Men: ≥1.7 mg/dL (150 µmol/L)
    • Women: ≥1.5 mg/dL (130 µmol/L)
  – On dialysis: hemodialysis or peritoneal dialysis
• Age ≥40 years
• No history of myocardial infarction or coronary revascularization
• Uncertainty: LDL-lowering treatment not definitely indicated or contraindicated
SHARP: Major Atherosclerotic Events

526 (11.3%) vs. 619 (13.4%) MAEs
Risk ratio 0.83 (0.74-0.94)
Logrank 2P=0.0021
<table>
<thead>
<tr>
<th>Outcome</th>
<th>Eze/simva</th>
<th>Placebo</th>
<th>RR</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Major atherosclerotic event</td>
<td>526</td>
<td>619</td>
<td>0.83</td>
<td>0.74-0.94</td>
</tr>
<tr>
<td>Vascular death</td>
<td>361</td>
<td>388</td>
<td>0.93</td>
<td>0.80-1.07</td>
</tr>
<tr>
<td>Non-vascular death</td>
<td>668</td>
<td>612</td>
<td>1.09</td>
<td>0.98-1.21</td>
</tr>
<tr>
<td>Cancer</td>
<td>438</td>
<td>439</td>
<td>0.99</td>
<td>0.87-1.13</td>
</tr>
<tr>
<td>Other SAEs</td>
<td>3258</td>
<td>3270</td>
<td>0.98</td>
<td>0.93-1.03</td>
</tr>
<tr>
<td>Category</td>
<td>eze/simva (n=4650)</td>
<td>placebo (n=4620)</td>
<td>RR (95% CI)</td>
<td></td>
</tr>
<tr>
<td>----------------------------------</td>
<td>--------------------</td>
<td>-----------------</td>
<td>------------------</td>
<td></td>
</tr>
<tr>
<td>Other cardiac</td>
<td>526 (11.3%)</td>
<td>557 (12.1%)</td>
<td>0.94 (0.83 – 1.05)</td>
<td></td>
</tr>
<tr>
<td>Other vascular (excl. cardiac)</td>
<td>324 (7.0%)</td>
<td>367 (7.9%)</td>
<td>0.88 (0.76 – 1.02)</td>
<td></td>
</tr>
<tr>
<td>Cancer (not incident)</td>
<td>73 (1.6%)</td>
<td>63 (1.4%)</td>
<td>1.15 (0.82 – 1.61)</td>
<td></td>
</tr>
<tr>
<td>Other renal</td>
<td>1958 (42.1%)</td>
<td>1966 (42.6%)</td>
<td>0.98 (0.92 – 1.04)</td>
<td></td>
</tr>
<tr>
<td>Respiratory</td>
<td>654 (14.1%)</td>
<td>666 (14.4%)</td>
<td>0.98 (0.88 – 1.09)</td>
<td></td>
</tr>
<tr>
<td>Liver/Pancreas/Biliary</td>
<td>82 (1.8%)</td>
<td>76 (1.6%)</td>
<td>1.08 (0.79 – 1.47)</td>
<td></td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td>957 (20.6%)</td>
<td>988 (21.4%)</td>
<td>0.96 (0.87 – 1.04)</td>
<td></td>
</tr>
<tr>
<td>Skin</td>
<td>238 (5.1%)</td>
<td>240 (5.2%)</td>
<td>0.99 (0.82 – 1.18)</td>
<td></td>
</tr>
<tr>
<td>Genital &amp; breast</td>
<td>176 (3.8%)</td>
<td>185 (4.0%)</td>
<td>0.94 (0.77 – 1.16)</td>
<td></td>
</tr>
<tr>
<td>Psychiatric</td>
<td>68 (1.5%)</td>
<td>62 (1.3%)</td>
<td>1.09 (0.78 – 1.54)</td>
<td></td>
</tr>
<tr>
<td>Neurological</td>
<td>220 (4.7%)</td>
<td>222 (4.8%)</td>
<td>0.99 (0.82 – 1.19)</td>
<td></td>
</tr>
<tr>
<td>Musculoskeletal</td>
<td>483 (10.4%)</td>
<td>471 (10.2%)</td>
<td>1.02 (0.90 – 1.16)</td>
<td></td>
</tr>
<tr>
<td>Hematological</td>
<td>224 (4.8%)</td>
<td>200 (4.3%)</td>
<td>1.12 (0.92 – 1.35)</td>
<td></td>
</tr>
<tr>
<td>Eye</td>
<td>184 (4.0%)</td>
<td>179 (3.9%)</td>
<td>1.02 (0.83 – 1.25)</td>
<td></td>
</tr>
<tr>
<td>Ear, Nose, Throat</td>
<td>72 (1.5%)</td>
<td>82 (1.8%)</td>
<td>0.87 (0.64 – 1.20)</td>
<td></td>
</tr>
<tr>
<td>Endocrine</td>
<td>58 (1.2%)</td>
<td>39 (0.8%)</td>
<td>1.47 (0.99 – 2.19)</td>
<td></td>
</tr>
<tr>
<td>Other medical</td>
<td>891 (19.2%)</td>
<td>896 (19.4%)</td>
<td>0.99 (0.90 – 1.09)</td>
<td></td>
</tr>
<tr>
<td>Non-medical</td>
<td>340 (7.3%)</td>
<td>333 (7.2%)</td>
<td>1.02 (0.88 – 1.19)</td>
<td></td>
</tr>
<tr>
<td><strong>ANY OF ABOVE</strong></td>
<td>3258 (70.1%)</td>
<td>3270 (70.8%)</td>
<td>0.98 (0.93 – 1.03)</td>
<td></td>
</tr>
</tbody>
</table>

*Excludes: MVEs, incident cancer, TIA, hospitalization with angina or heart failure, dialysis access revision, diabetes and hypoglycaemia, dialysis or renal transplantation, pancreatitis, hepatitis, gallstone events, myopathy and rhabdomyolysis
QbD approach to antibacterial drug development: FOCUS on the IMPORTANT

* Important Question
  * Is this new drug effective (and safe)?

* Reliable Answer
  * Feasibility
    * Would I enter myself/relative/patient into this study?
    * Does this require additional work
  * Collect essential information efficiently
    * Avoid the temptation to add extras
    * Avoid errors through careful design
    * Check for errors that matter to decision making (participant safety / reliability of results)
QbD approach to antibacterial drug development: RECRUITMENT

* Inclusion
  * Likely to have relevant diagnosis (HABP/VABP)
  * Likely to have relevant organism
    * i.e. outlook good if treated with an effective agent
  * Likely to have relevant outcome
    * i.e. outlook poor if not treated appropriately

* Uncertainty
  * No definite indication for, or contraindication to, active or comparator treatment

* Feasibility
  * Methods must fit in to routine clinical pathway
QbD approach to antibacterial drug development: COMPLIANCE

* NB: Not possible to mandate against use of effective treatment

* Non-compliance:
  * Discontinuation of active treatment
  * Initiation of other effective treatments in either active or comparator arm
  * Loss to follow-up
    * e.g. after primary event or after stopping study treatment

* Implications:
  * Non-compliance reduces the difference between treatment groups
    * Conservative for superiority assessments
    * Counter-conservative for non-inferiority (including safety) assessments
QbD approach to antibacterial drug development: OUTCOMES & ANALYSIS

* Choice of outcome must be:
  * Clinically relevant
  * Objective
  * Assessed blind to treatment allocation
  * Likely to be affected by the randomized intervention

* Analysis
  * Intention-to-treat
  * Could be limited to pre-specified sub-group (e.g. based on bacteriology/sensitivities on baseline samples)
  * Avoid sub-group analyses that are
    * (a) underpowered,
    * (b) determined by factors recorded post-randomization, and/or
    * (c) data derived
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
Effect of ERN/LRPT on SERIOUS adverse events (median follow-up 3.9 years)

- **Diabetic complication**: ERN/LRPT 3.7% vs Placebo 1.8%, p < 0.0001
- **New onset diabetes**: ERN/LRPT 1.8% vs Placebo 1.0%, p < 0.0001
- **Infection**: ERN/LRPT 1.4% vs Placebo 0.4%, p < 0.0001
- **Gastrointestinal**: ERN/LRPT 1.0% vs Placebo 0.7%, p = 0.0008
- **Musculoskeletal**: ERN/LRPT 0.7% vs Placebo 0.3%, p = 0.0002
- **Heart failure**: ERN/LRPT 0.4% vs Placebo 0.7%, p = 0.05
- **Bleeding**: ERN/LRPT 0.7% vs Placebo 0.3%, p = 0.0026
- **Skin**: ERN/LRPT 0.3% vs Placebo 0.3%, p = 0.0026

Percentage of patients with SERIOUS adverse events.