More efficient evaluation using registries and Bayesian approaches

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## IDEAL framework

<table>
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<tr>
<th>1 Idea</th>
<th>2a Development</th>
<th>2b Exploration</th>
<th>3 Assessment</th>
<th>4 Long-term study</th>
</tr>
</thead>
<tbody>
<tr>
<td>Purpose</td>
<td>Proof of concept</td>
<td>Development</td>
<td>Learning</td>
<td>Assessment</td>
</tr>
<tr>
<td>Number and types of patients</td>
<td>Single digit; highly selected</td>
<td>Few; selected</td>
<td>Many; may expand to mixed; broadening indication</td>
<td>Many; expanded indications (well defined)</td>
</tr>
<tr>
<td>Number and types of surgeons</td>
<td>Very few; innovators</td>
<td>Few; innovators and some early adopters</td>
<td>Many; innovators, early adopters, early majority</td>
<td>Many; early majority</td>
</tr>
<tr>
<td>Output</td>
<td>Description</td>
<td>Description</td>
<td>Measurement; comparison</td>
<td>Comparison; complete information for non-RCT participants</td>
</tr>
<tr>
<td>Intervention</td>
<td>Evolving; procedure inception</td>
<td>Evolving; procedure development</td>
<td>Evolving; procedure refinement; community learning</td>
<td>Stable</td>
</tr>
<tr>
<td>Method</td>
<td>Structured case reports</td>
<td>Prospective development studies</td>
<td>Research database; explanatory or feasibility RCT (efficacy trial); disease-based (diagnostic)</td>
<td>RCT with or without additions/ modifications; alternative designs (eg, SCOAP, STS, NSQIP); rare-case reports</td>
</tr>
<tr>
<td>Outcomes</td>
<td>Proof of concept; technical achievement; disasters; dramatic successes</td>
<td>Mainly safety; technical and procedural success</td>
<td>Safety; clinical outcomes (specific and graded); short-term outcomes; patient-centred (reported) outcomes; feasibility outcomes</td>
<td>Clinical outcomes (specific and graded); middle-term and long-term outcomes; patient-centred (reported) outcomes; cost-effectiveness</td>
</tr>
<tr>
<td>Ethical approval</td>
<td>Sometimes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Examples</td>
<td>NOTES video</td>
<td>Tissue engineered vessels</td>
<td>Italian D2 gastrectomy study</td>
<td>Swedish obese patients study</td>
</tr>
</tbody>
</table>

RCT = randomised controlled trial. SCOAP = Surgical Clinical Outcomes Assessment Programme. STS = Society of Thoracic Surgeons. NSQIP = National Surgical Quality Improvement Program. NOTES = natural orifice transmural endoscopic surgery.

Table: Stages of surgical innovation
Classic scenario

It’s always too early (for rigorous evaluation) until, suddenly, it’s too late!

(Martin Buxton)
Narrow window of opportunity

- Wish for rapid progression to full implementation once early efficacy shown - skip I DEAL stage 3

The challenge...
- How can we evaluate rigorously BUT efficiently?
The challenge with the RCT

- Rigorous - yes
- Randomisation is the key ingredient

But... often perceived to be:
- Lengthy
- Overly burdensome & lots of data collection
- Requires lots of stand-alone infrastructure
- Requires unrealistic numbers of patients
Can we be smarter?

- If an RCT thought to be infeasible, do we have any options?
- Want to ensure we keep randomisation - the “pearl” of the RCT
- Can we make the infrastructure easier?
Example – the REBOA trial

- **REBOA** - Resuscitative Endovascular Balloon Occlusion of the Aorta
- **Device for management of exsanguinating haemorrhage after major trauma**
REBOA & I DEAL

• I DEAL 2a and 2b studies reported:
  – some good observational designs incl. propensity matched studies

• Conflicting evidence:
  – some studies showing benefit; however, others showing possible harm

• Clinical community see new device as beneficial

• High profile cases documented in news

• Initial perception – surely doing something better than nothing
Health

Balloon surgery stops fatal bleeding at roadside

By Smita Mundass
Health reporter, BBC News

© 17 June 2014 | Health

The moment a cyclist bleeding to death was saved - by a balloon fed through her leg: Woman, 24, undergoes emergency procedure after doctors decide she would not survive journey to hospital.

London's Air Ambulance crew have become the first team in the world to use a balloon device to control catastrophic bleeding at the roadside.
Dilemma

- Clinical community want to go straight to implementation
- Evaluators wish to conduct IDEAL Stage 3 RCT especially as some prior conflicting evidence

- Compromise...
  - Short window of evaluation
Classical RCT design

- **Primary outcome** - 90 day mortality
- **Current 90 day mortality estimate** = 33.5%
- **To detect 5% absolute reduction** ($\alpha = 5\%$; 80% power) requires 2684 patients
- **Only ~ 125 possible patients in England every year**
- **Over 20 years to recruit**
- **NOT FEASIBLE!**
Options

- Easy option
  - skip evaluation

- Alternative?
  - Bayesian trial design?
Bayesian trial design

- Fundamentally different to classical RCT
- Gives the probability of a specific treatment effect *given observed data*
- Probability based decision-framework - parallels with HTA decision-making
- Generates iterative estimates of effect - combines prior information with accruing data
- Properties can be modelled for any sample size
Bayesian approach

- Start with feasible sample size
- Set preferred rules
- Model design characteristics
- Decide if acceptable to clinicians, trialists and funders
- If yes, then feasible

Bayesian approach - outlines what you *can* say with the data you have available
Bayesian approach for REBOA

- Feasible sample size 120 (2 year recruitment)
- Rules: maximise the probability to stop early if signal for harm - three planned analyses

The probabilities of early stopping are:
- high if REBOA results in markedly decreased 90-day survival and roughly 19% if there is no difference to standard care
- below 10% if REBOA is a success with OR $\geq 1.05$

The probability that success is declared:
- is less than 2% if REBOA is harmful
- exactly 5% if both treatments are equal
- over 60% if REBOA does well (OR $\geq 1.2$)
- over 90% if it does exceptionally well (OR $\geq 1.3$)
Implications for REBOA study

- Transformed infeasible study into feasible study
- Retained randomisation - maximised rigour
- Still requires meticulous planning

However ...

- Judgement required: are the design characteristics “good enough” to allow clinical decision-making?
Smart data collection

- National registry for all major trauma patients - TARN
- Designed REBOA trial data to map onto routine TARN data collection - requires good collaboration with the registry owners
- ALL trial data (except randomisation in the ER) collected using routine infrastructure
- Minimises extra work for clinicians (and patients)
Implications for IDEAL

- Stage 3 – often squeezed

Options for making Stage 3 smarter ...

- Retain randomisation wherever possible
- Evaluations can be made more efficient through planned use of registries
- Using a Bayesian trial design can allow an RCT where conventional approaches seem infeasible

  However, not a panacea - requires careful thought and planning & may still decide not feasible
Further literature

- FDA guidance on use of Bayesian stats for medical device Clinical Trials:
  
  https://www.fda.gov/MedicalDevices/ucm071072.htm

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