More efficient evaluation using registries and Bayesian approaches

Marion Campbell

Trialist & Statistician

Professor of Health Services Research

Dean of Research for Life Sciences & Medicine, University of Aberdeen

@marionkcampbell

Health Services Research Unit
University of Aberdeen

HSRU is core funded by the Chief Scientist Office of the Scottish Government Health and Social Care Directorates. The author accepts full responsibility for this talk.

IDEAL framework

	1 Idea	2a Development	2b Exploration	3 Assessment	4 Long-term study
Purpose	Proof of concept	Development	Learning	Assessment	Surveillance
Number and types of patients	Single digit; highly selected	Few; selected	Many; may expand to mixed; broadening indication	Many; expanded indications (well defined)	All eligible
Number and types of surgeons	Very few; innovators	Few; innovators and some early adopters	Many; innovators, early adopters, early majority	Many; early majority	All eligible
Output	Description	Description	Measurement; comparison	Comparison; complete information for non-RCT participants	Description; audit, regional variation; quality assurance; risk adjustment
Intervention	Evolving; procedure inception	Evolving; procedure development	Evolving; procedure refinement; community learning	Stable	Stable
Method	Structured case reports	Prospective development studies	Research database; explanatory or feasibility RCT (efficacy trial); diseased based (diagnostic)	RCT with or without additions/ modifications; alternative designs	Registry; routine database (eg, SCOAP, STS, NSQIP); rare-case reports
Outcomes	Proof of concept; technical achievement; disasters; dramatic successes	Mainly safety; technical and procedural success	Safety; clinical outcomes (specific and graded); short-term outcomes; patient-centred (reported) outcomes; feasibility outcomes	Clinical outcomes (specific and graded); middle-term and long-term outcomes; patient-centred (reported) outcomes; cost-effectiveness	Rare events; long-term outcomes; quality assurance
Ethical approval	Sometimes	Yes	Yes	Yes	No
Examples	NOTES video[6]	Tissue engineered vessels[7]	Italian D2 gastrectomy study[8]	Swedish obese patients study[9]	UK national adult cardiac surgical database[10]

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

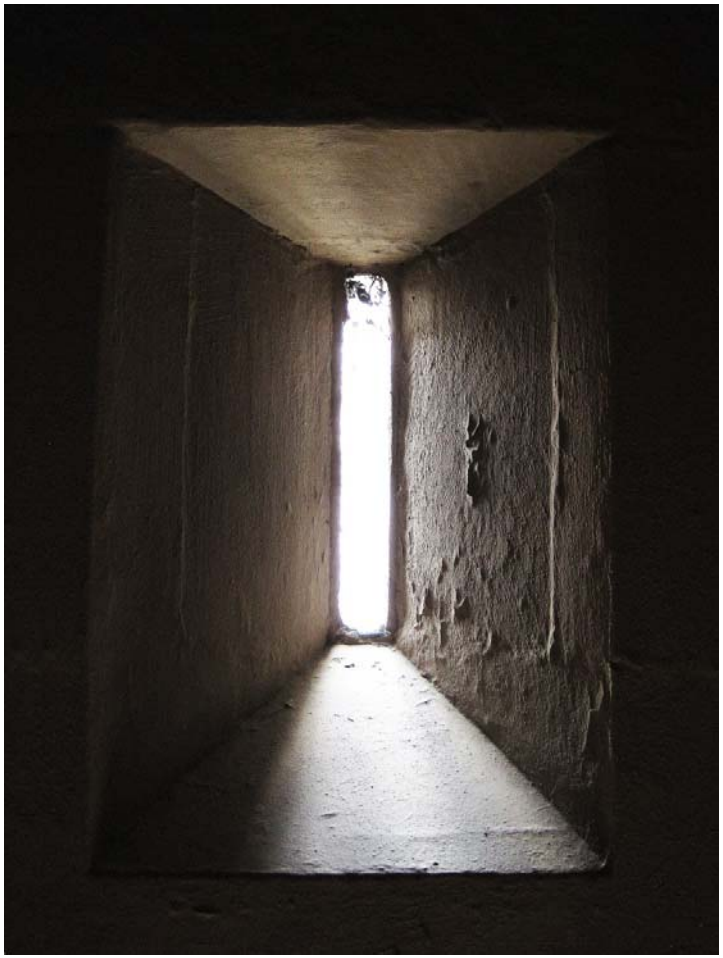
Table: **Stages of surgical innovation**

Classic scenario

It's always too early (for rigourous 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 IDEAL 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:

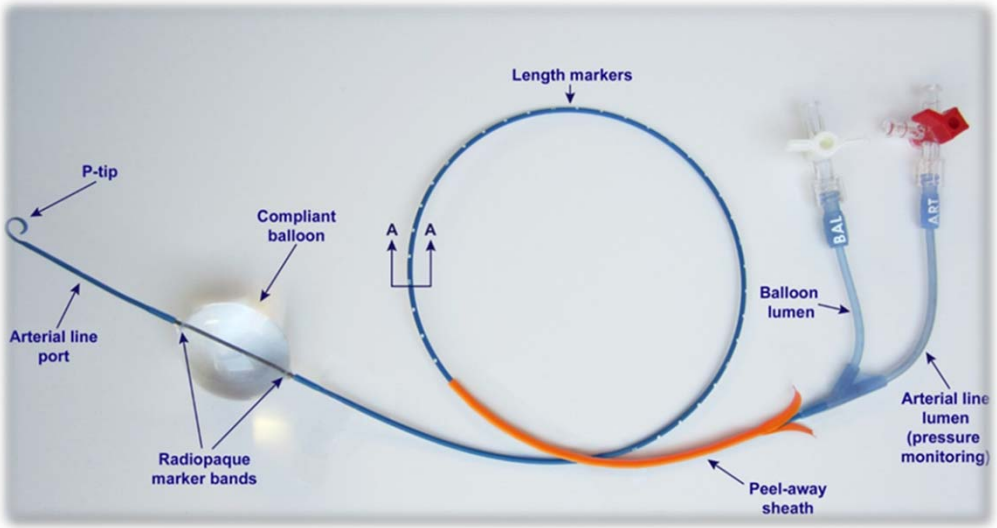
- Lengthy
- Overly burdensome & lots of data collection
- Requires lots of stand-alone infrastructure
- Requires unrealistic numbers of patients

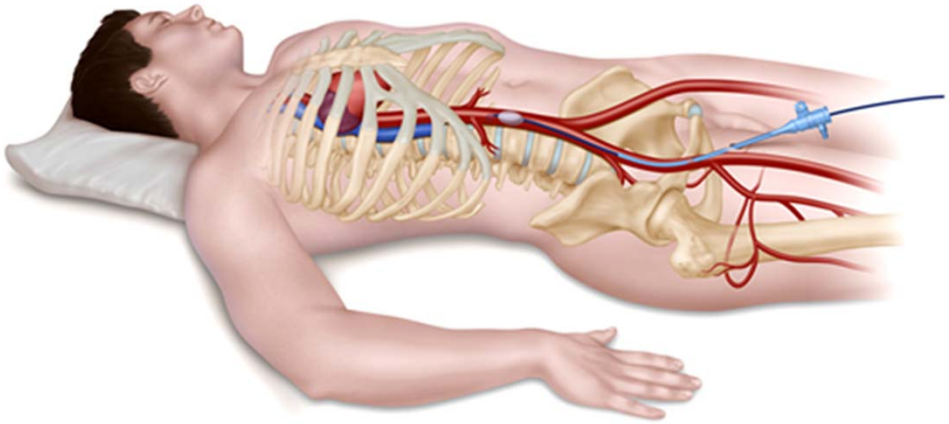
Can we be smarter?

- 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 & IDEAL

- IDEAL 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

BBC Sign in

News | Sport | Weather | iPlayer | TV | Radio

NEWS

Home | UK | World | Business | Politics | Tech | Science | Health | Education | Entertainment

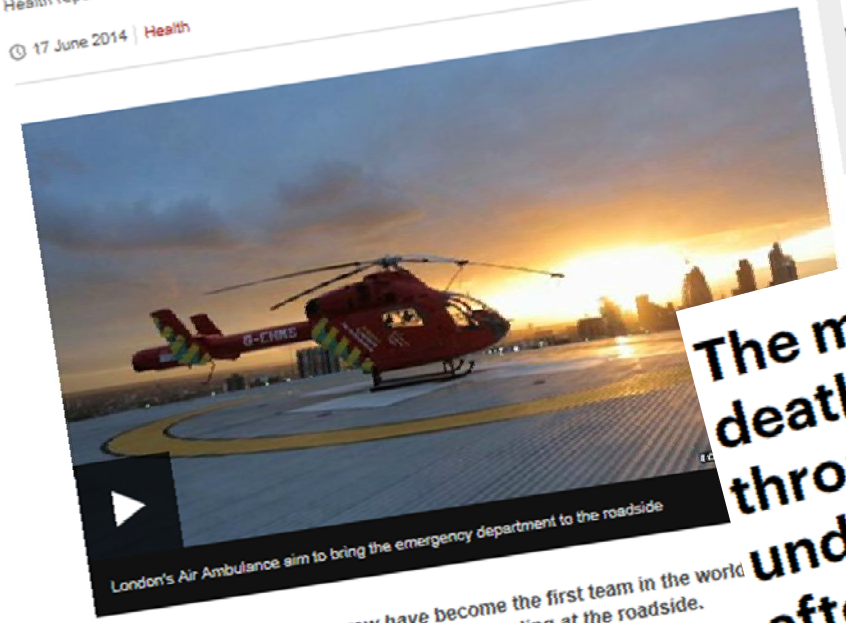
Health

Balloon surgery stops fatal bleeding at roadside

By Smitha Mundasad
Health reporter, BBC News

Share

17 June 2014 | Health



London's Air Ambulance aim to bring the emergency department to the roadside

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.

Emergency Medicine News

THE MOST TRUSTED NEWS SOURCE IN EMERGENCY MEDICINE

Collections | CME | eNews | Past Issues | Blogs | Videos | Podcasts | Info & Services

Previous Article | Next Article >

ews: New REBOA Catheter a Game-Changer for Trauma

se, Joseph MD

ency Medicine News: May 2018 - Volume 33 - Issue 5 - pp 1,29–29

1097/01.EEM.0000483170.27856.cd

nformation

physicians are probab

orta (REBOA)

partm

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

Dilemma

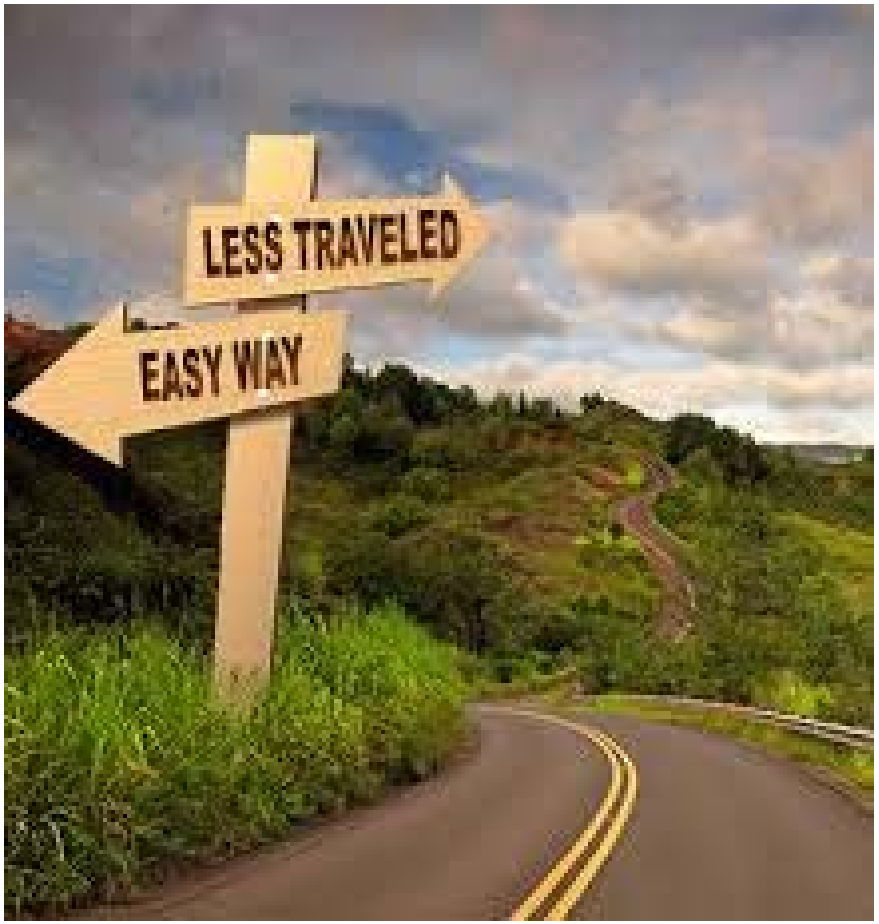
- Clinical community want to go straight to implementation
- Evaluators wish to conduct IDEAL Stage 3 RCT especially as some prior conflicting evidence

- 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 (α = 5%; 80% power) requires 2684 patients
- Only ~ 125 possible patients in England every year
- Over 20 years to recruit
- NOT FEASIBLE!

Options

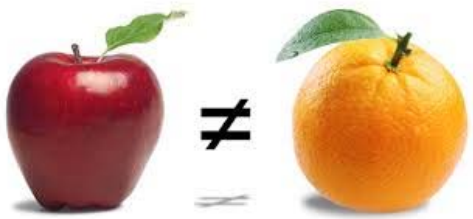


- **Easy option**
  – skip evaluation

- **Alternative?**
  – Bayesian trial design?

Bayesian trial design

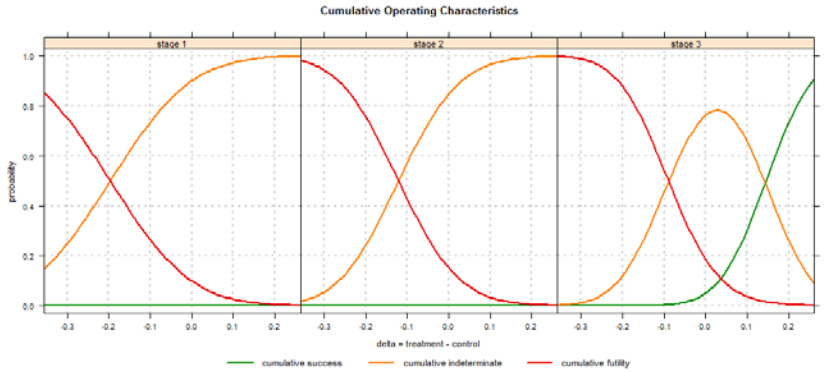
- **Fundamentally different to classical RCT**



- **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≥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 ≥1.2)
- over 90% if it does exceptionally well (OR ≥1.3)

Implications for REBOA study

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

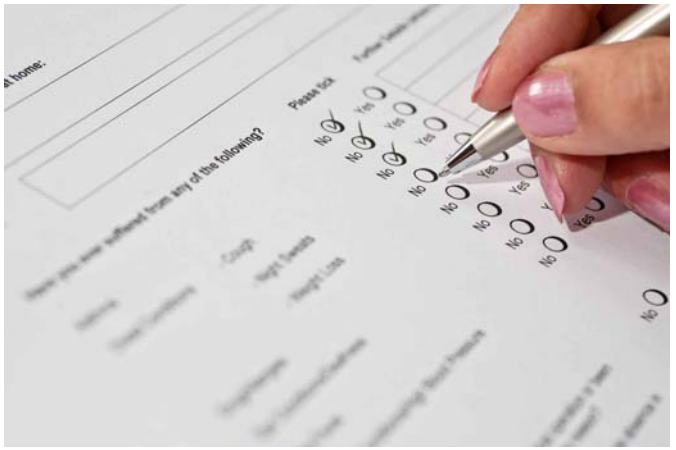
However …

- 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)

TARN
THE TRAUMA AUDIT & RESEARCH NETWORK



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

- **Berry DA. Bayesian Clinical Trials. *Nature Reviews Drug Discovery* 2006; 5: 27-36**

Acknowledgements

Thank you for your attention

Contact details:

- **m.k.campbell@abdn.ac.uk**
- **@marionkcampbell**

The UK-REBOA trial has been funded by the NIHR HTA programme (ref no 14/199/09)