Challenges in Surgical Trials

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<table>
<thead>
<tr>
<th></th>
<th>Pfizer</th>
<th>Intuitive Surgical</th>
<th>Cambridge Medical Robotics</th>
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</thead>
<tbody>
<tr>
<td>Educational grants/funding</td>
<td>X</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Consultancy</td>
<td></td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>Travel expenses</td>
<td></td>
<td>X</td>
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<tr>
<td>Honoraria/Speaker fees</td>
<td>X</td>
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</table>
’Heal with steel’

- One-third of hospital admissions, surgical
- 15.2 million new cases of cancer in 2015, over 80% of cases will need surgery, some several times
- Surgery is the cancer treatment with greatest impact on long term survival in most cancers
- Surgery significantly improves symptoms in palliative scenarios
- Surgery contributes to 49% cases where cancer is cured
Surgical trials – a broad church

• Device trials
• Window-of opportunity trials
• Neoadjuvant and adjuvant studies
• Surgical technique trials
• Surgery vs ablation/radiation studies
Surgeons have a key role in research

Figure 2. Roles a surgeon may take on in cancer research

- Design and evaluation of surgical interventions or technologies (‘surgical researcher’ role)
- Design and evaluation of perioperative clinical interventions (‘multidisciplinary researcher’ role)
- Recruitment of surgical patients into trials (‘recruiter’ role)
- Collecting tissue samples or data for research (‘sample/data collector’ role)
- Design and delivery of translational research (‘translational researcher’ role)
- Design and delivery of laboratory research (‘basic scientist’ role)

Work can be shared across disciplines
95% of surgical consultants have never randomised a patient into a trial
Lack of trials
Surgical research or comic opera: questions, but few answers

Richard Horton
*The Lancet*, London, UK

By far the most common investigative method was the case series (80 papers, 46%). The next most common category of study was laboratory animal experimentation (31, 18%). The importance of the case series in surgical research is beyond doubt. Therefore, it seems reasonable to ask whether we can trust this study method to yield a valid result. According to conventional epidemiological wisdom, the answer is no.

The advantages of case series are that they are cheap, quick, and easy to perform; that they generate valuable hypotheses for future investigation; and that they encourage detailed descriptive reports that are often essential for defining new diseases, such as AIDS. However, case series provide the weakest evidence for assessing the efficacy of a treatment or for establishing causation. Some critics may not even regard the case series as research at all, rating unplanned observations as hopelessly invalid—the risk of uncontrolled bias and confounding are potentially lethal flaws.
The need to improve

• Better inform clinical practice, changes often happen in leaps (robotics), we need to be well positioned to evaluate

• Only one in eight studies published in a major urologic journal provides high-level evidence (1 or 2)

• Bulk of our practice is based on limited information from retrospective case series
And 21% surgical trials are discontinued...

• 1 in 5 surgical randomised controlled trials was stopped early and 1 in 3 completed trials did not publish

• Commonest reason for discontinuation is poor recruitment (usually identified rapidly after opening)

• Futility (i.e. new conclusive data emerges)

• Clinically irrelevant questions, comparisons and outcomes

• Biases from previous eras (i.e. immunotherapy/CNx in mRCC)

Chapman BMJ 2014; 340: g6870
Problems with randomised trials in surgery

- Surgeon and patient equipoise
- Personal prestige
- Lack of funding
- Infrastructure and experience in data collection
- Rare conditions
- Life threatening and urgent situations
- Operative learning curves
- Blinding

McCulloch BMJ 2002; 324:1448
**Lack of funding**

![Figure 6: Number of awards and spend on surgical cancer research by NCRI Partners in 2010](image)

<table>
<thead>
<tr>
<th>Number of awards</th>
<th>Spend</th>
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<tbody>
<tr>
<td>Number of awards in NCRI database*</td>
<td>£404.2 million</td>
</tr>
<tr>
<td>Number of surgical research awards</td>
<td>£11.4 million</td>
</tr>
<tr>
<td>Surgical question</td>
<td>£6.4 million</td>
</tr>
<tr>
<td>Research in surgical setting</td>
<td>£4.5 million</td>
</tr>
<tr>
<td>Personal award</td>
<td>£0.4 million</td>
</tr>
<tr>
<td>Surgical research awards as a percentage of all awards</td>
<td>3.7%</td>
</tr>
<tr>
<td>Surgical research spend as a percentage of total spend</td>
<td>2.8%</td>
</tr>
</tbody>
</table>

*Excludes 158 awards that support core/centre funding across multiple disciplines where the surgical component could not be estimated, with a value of £100.0 million.
HEAD TO HEAD

Should surgical training include involvement in a clinical trial?

YES

Clinical trials in surgery are sometimes perceived as a luxury—difficult to perform, costly, informative, and certainly activities that should be restricted to academics. Despite challenges, the benefits that surgical trials bring can be substantial, enabling safe and controlled evaluation and dissemination of new techniques and technologies. The rapid proliferation of new technologies is increasing the demand for research, and many clinicians will be needed to run these clinical trials, way more than the number in academic units. Surgical training, the next generation of consultants, will be formed by their trainers if they are competent and confident clinicians. Without specific training, there is little chance that any surgeon is capable or willing to undertake research with accuracy.

The promise of new technologies and the demand for clinical trials will increase many clinicians will be needed. This will lead away from the academic units in which they train.

Morten Blech, professor of surgery, Academic Department of Surgery, University Hospital of Birmingham, UK (blech.morten@bham.ac.uk)

NO

The premise of this question is that all surgical training might benefit from taking part in a clinical trial. Although at face value this would seem to be a laudable training goal, there are several considerations. First and foremost is that of balancing the needs of the trainee. Surgery is a craft specialty, and training in the technical and team skills needed to provide the best quality surgical outcomes and lead a theatre team must be the primary aim of training.

We fail a landscape.

With the European Working Time Directive, the new contract in the United Kingdom, and rising public expectations, the time available to surgical trainees to learn their craft in theatre is being eroded, and we risk a landscape. The numbers of lifetime cases, exposures, and complications are rising, especially for surgeons who have just started independent practice. Trainees are left swirling at night worrying about getting the top clamp on a ruptured aneurysm or whether they

Not part of our culture

Iterative trial and error—a process of learning

In all likelihood the trainee will join a multicentre trial that is already set up at their site, recruit a few patients, and leave the site again before the reporting phase...
Urology and RCC surgical trials
Medical expulsive therapy in adults with ureteric colic: a multicentre, randomised, placebo-controlled trial

Prof Robert Pickard, MDa, Kathryn Starr, MSbc, Graeme MacLennan, MScb, Thomas Lam, PhDc, Ruth Thomas, PhDb, Jennifer Burr, MDc, Gladys McPherson, PhDb, Alison McDonald, MScb, Kenneth Anson, MSa, Prof James N'Dow, MDb, Neil Burgess, MChb, Terry Clarkh, Mary Kilonzo, MScd, Katie Gillies, PhDb, Kirsty Shearer, PhDb, Charles Boachie, BSbc, Sarah Cameron, MPharmdb, Prof John Norrie, MScb, Prof Samuel McClinton, MDc, i, a, b, c, d, e, f, g, h, i, j, k, l, m, n, o, p, q, r, s, t, u, v, w, x, y, z

Jan 11, 2011 to Dec 20, 2013, 1167 randomised participants
Extremely well funded, allowing innovating recruitment
Feasibility Study of Partial Nephrectomy (Radiofrequency Ablation/Cryotherapy) for SRMs

- 60 patients target
- Only £80,000 from CRUK
- Only 24 months
- Only 6 centres (4 opened)
- D0 only 1 centre open
- 140 patients screened, but (mainly) due to surgeon/radiologist objection (rather than patient) only 23 patients randomised

Top tip with the knowledge of time to open studies in your centre. Be realistic about recruitment in your centre. Trials nurse (and PI) should screen every SRM patient in the MDM, ask the question!
Dissecting out the issues
RCC Trial and Urologist Engagement Challenges

1. Lack of surgical renal cancer trials in the portfolio
2. Little knowledge of what renal cancer surgeons in UK want/can deliver trial wise
3. Lack of engagement of UK RCC surgeons (20% renal cancer surgeons engaged)
4. Little/no urology trainee education/involvement in trials (11/150 delegates at Tomorrow’s Leaders course)
5. Only 14% urological cancer patients had trials discussed with them (National Cancer Patient experience)
UK RCC Surgeon Survey

• BAUS provided list of urologists performing >20 RCC operations/annum

• 136 urologists emailed, 63 responses (46%)

• 0 academics, 32% have honorary academic status
Non recruiters

- 56% no suitable trials
- 22% realm of oncologist
- 33% no time
- 22% no recognition
- 22% no infrastructure

- ‘perceived hassle, lack of time, many hoops to jump through’
- ‘Centralisation of specialist surgery and significant time constraints due to pressures from emergency and non-renal surgery obligations’
Recruiters

• 21% **DID** get recognition for recruitment to trials:
  • Co-authorships
  • Awards
  • Co-I status
  • Evidence for CEAs
  • PA
  • Appraisal evidence

• 74% have **NO time** in job plan for research, although only 33% said this was very likely to prevent involvement

• 60% said **up to date information** influenced involvement
IDEAL (Idea, Development, Exploration, Assessment, Long term study) framework for surgical innovation

Table 1 | IDEAL framework and recommendations for surgical innovation. More details are available at http://www.ideal-collaboration.net/

<table>
<thead>
<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>Question</td>
<td>Can the procedure or device achieve a specific physical or physiological goal?</td>
<td>What is the optimal technique or design, and for which patients does it work best?</td>
<td>What are the outcomes of more widespread use? Can consensus equipoise be reached on a trial question?</td>
<td>How well does the procedure work compared with current standards of care?</td>
</tr>
<tr>
<td>Key outcome</td>
<td>Proof of concept</td>
<td>Safety, efficacy</td>
<td>Efficacy</td>
<td>Comparative effectiveness</td>
</tr>
<tr>
<td>Patient base</td>
<td>Single to few (&lt;10)</td>
<td>10s</td>
<td>100s</td>
<td>100s+</td>
</tr>
<tr>
<td>Recommendations for study design and reporting</td>
<td>First-in-human study; case report (structured); confidential registration of all first-in-human procedures</td>
<td>Prospective development study—cohort study with sequential reporting of cases and modifications</td>
<td>Prospective exploratory study—a collaborative cohort study with learning curve evaluation or feasibility RCT</td>
<td>Randomised controlled trial</td>
</tr>
<tr>
<td>Example of procedure at this stage</td>
<td>Uterine transplant with successful live birth</td>
<td>Peroral endoscopic myotomy for oesophageal achalasia</td>
<td>Complex endovascular stenting, such as in complex aortic aneurysms</td>
<td>Minimally invasive oesophagectomy</td>
</tr>
</tbody>
</table>

Sedrakyan et al. BMJ 2016;353:i2372
The struggle for better research in surgery

Two decades ago, a Comment in The Lancet questioned the quality of research in surgery. What has changed since then? On the one hand, much has improved; on the other, little. Thanks to initiatives like the IDEAL Collaboration (an indirect outcome of the 1996 Comment), the recognition that evidence is needed to drive improvements in surgical care is broadly recognised; though imperfectly implemented. How evidence is acquired remains problematic, attributable to the paucity of universal outcome measures, a perceived undervaluing of technical skill, and widespread denial of equipoise. The result is an uneasy research culture that is inconsistent in converting intellectual curiosity into sound science.

Two recent meetings provide insight. Despite the IDEAL Collaboration’s leadership as a champion for evaluation, the audience at its conference in Oxford on April 7–8 epitomised the wide distribution of attitudes among surgeons. Although many were keen to extend rigorous evaluation to surgical devices, others appeared comfortable with retrospective case series as proof of benefit. A month later, the National Cancer Research Institute hosted an expert meeting on surgical research outcomes at the Royal College of Surgeons, London, UK. It was the first of five workshops on the future of surgery, stimulated by genuine concern about the UK’s capacity to undertake surgical research. The gathering was notable for the engagement of funders and patient representatives, who articulated clearly that advances in surgical care depend upon strong networks of clinical investigators.

Compared with 1996, there is a perceptible change in tune among leading surgeon-researchers. For instance, the welcome (if not yet common) use of randomised controlled trials in surgery provides a sound rebuttal to those who cling to the notion of surgical exceptionalism. And, as Jeffrey Lawson and colleagues show in their Article on vascular grafts in today’s issue, even modestly sized IDEAL stage 2a observational studies have the power to change thinking when done well. If research in surgery is to deliver clear answers for surgeons and their patients, then the culture of innovation, the hallmark of surgery, needs to be firmly coupled with evaluation, the bedrock of evidence. ■ The Lancet
Conclusions

• Trials need to be desired and deliverable by full time clinical colleagues

• Pilot/feasibility studies are ideal starting points

• Become one of the 5% who recruit and you can change surgical treatment paradigms