IDEAL framework for surgical innovation 3: randomised controlled trials in the assessment stage and evaluations in the long term study stage

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The complexity of surgical procedures often poses challenges for conducting a rigorous and comprehensive evaluation. This paper considers the final two IDEAL stages of surgical innovation. Surgical randomised controlled trials are often challenging to undertake and require careful consideration of the intervention definition, who should deliver it, and the impact of surgeon and patient preferences. In the long term study stage, better monitoring of surgical procedures is needed, along with improved surveillance of devices.

Introduction

The IDEAL framework describes the stages through which interventional therapy innovation normally passes: idea, development, exploration, assessment, and long term follow-up (also known as stages 1, 2a, 2b, 3, and 4, respectively). This paper focuses on the stages of assessment (specifically in relation to randomised trials) and long term follow-up. By the assessment stage, a new intervention will have shown early promise and be used increasingly by the surgical community; however, the intervention’s relative benefit compared with alternative approaches will have not had the anticipated influence on the adoption of the intervention. Even if a trial evaluation is undertaken successfully, factors out of the study investigators’ control have not had the anticipated influence on the adoption of the intervention. While several surgical trials have been successful and influential, others have been attempted and failed or have not had the anticipated influence on the adoption of the intervention. Even if a trial evaluation is undertaken successfully, factors out of the study investigators’ control (for example, innovations and technological changes) can lead to uncertainty about the evaluation’s applicability. Another challenge is to measure outcomes comprehensively; surgical studies are also limited by their selection of outcomes, which are often short term, “operation” focussed, and inconsistently defined. Properly conducted randomised controlled trials and observational studies with agreed and defined core outcomes are needed at these critical stages. The failure to conduct methodologically rigorous studies has resulted in some surgical interventions becoming and remaining standard practice without good evidence. Similarly, new medical devices are widely used without due assessment. In this paper, we consider in turn the roles of randomised controlled trials in the assessment stage and evaluations in the long term stage.

Randomised controlled trials in the assessment stage

The role of randomised controlled trials in evaluating surgical interventions has been debated over the past 30 years. A consensus in favour of accepting properly conducted trials as the “gold standard” for comparisons of efficacy and effectiveness between surgical procedures has eventually emerged, although not without controversy. While several surgical trials have been successful and influential, others have been attempted and failed or have not had the anticipated influence on the adoption of the intervention. Even if a trial evaluation is undertaken successfully, factors out of the study investigators’ control (for example, innovations and technological changes) can lead to uncertainty about the evaluation’s applicability. The assessment stage provides a window of opportunity—albeit sometimes a brief one—to obtain definite randomised evidence about effectiveness. The IDEAL framework proposes that a large multicentre trial is most valuable and viable during the assessment stage, although small single centre trials might appear as early as IDEAL stage 2a. Randomised controlled trials have an array of potential problems in evaluating surgical techniques (box 1), and most stem from three related issues: the intervention definition, who delivers the intervention, and the treatment preferences of surgeons and patients.

Box 1 | Potential solutions to overcome common variations in surgical randomised controlled trials

| Surgeon preferences |
|---------------------|
| Maximise flexibility in the delivery of surgical interventions, beyond the key distinctive elements, to allow for variation in surgeon and centre practices |
| Implement recruitment of participants by a third party |
| Use broad patient eligibility criteria |
| Undertake preliminary work to establish consensus regarding community uncertainty |
| Adopt an expertise based trial design |

| Patient preferences |
|---------------------|
| Undertake a qualitative evaluation of patients’ perspectives and experiences |

| Quality control of the intervention |
|-----------------------------------|
| Use criteria for surgeon eligibility (for example, training and previous number of cases) |
| Record an objective measure of quality (for example, lymph node yield for gastric cancer surgery) |
| Record indicators of surgical decision making (for example, conversion from partial to total knee replacement, or from laparoscopic to open surgery) |
## Surgical trials examples—standardisation of interventions and eligibility criteria of patients and surgeons

| Research question                                      | No of centres | Patient/surgeon eligibility                                                                 | Standardisation of interventions                                                                 | Perioperative care                                                                 | Preoperative and postoperative care |
|--------------------------------------------------------|---------------|--------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------|------------------------------------|
| Stapler v hand sewn closure after distal pancreatectomy (DOSPACT) | 21            | Broad/training given to all participating surgeons (centre had to perform 10 pancreatic resections per year) | Resection and closure procedures standardised; staple specified; type of incision not standardised; no additional intraoperative treatment or covering of the pancreatic remnant; splenectomy in addition to distal pancreatectomy at discretion of surgeon; standardised policy in relation to osteosilde use at sites; pain management not standardised | Bowel preparation not standardised; standardised drain use; recovery not standardised (for example, location, feeding, and mobilisation) |
| Treatment of tibial fractures with reamed or non-reamed intramedullary nails (SPRINT) | 29            | Broad/no reported restrictions                                                               | Standardised reamed nailing and unreamed nailing procedures                                      | Standardised antibiotic use in open and closed fractures; standardised mobilisation (both open and closed) and use of growth stimulation not allowed during first 12 months; wound closure (open); dynamisation of the nail (both) and reoperation (open) only allowed in specific circumstances |
| Treatment of abdominal aortic aneurysm (EVAR trial 1) with endovascular or open repair | 34            | Broad/hospitals had to complete 20 endovascular repair procedures                             | Choice of EVAR device left to participating surgeons, otherwise no stated restrictions            | No stated restrictions                                                          |
| Treatment of premenopausal women with abnormal uterine bleeding with surgical or medical treatment (Ms study) | 2             | Broad/no stated restrictions                                                                 | Type and route of hysterectomy at discretion of surgeon, prophylactic oophorectomies were discouraged | No stated restrictions                                                          |
| Treatment of osteoarthritis of the knee with arthroscopic debridement, arthroscopic lavage, or placebo surgery | 1             | Broad/one surgeon performed all operations                                                   | Surgical interventions standardised                                                              | Standardised anaesthetic; mobilisation and pain management (analgesics)          |

### Intervention definition

How tightly the intervention should be defined will depend on the type of comparison (table). Trials investigating the auxiliary facets of the intervention are valuable, but studies evaluating the surgical core of an innovative procedure (whether a new procedure or a modification of an established procedure) are crucial. In a comparison of medical versus surgical trials, the definition of surgery can be broad. For example, in a trial of medical treatment versus hysterectomy, the type and route of the hysterectomy was left to the discretion of the gynaecologists, as was the medical treatment (although there was a suggested regimen). In a trial comparing open versus laparoscopic repair of inguinal hernia, surgeons were allowed to choose the type of open and laparoscopic repair. If special equipment is needed, the medical device used does not typically need to be not restricted. In trials of medical devices, or where the related procedures being compared are similar, it may be necessary to define each intervention precisely and to introduce process control measures to check on compliance to preclude contamination and control the effect of ancillary care. Small changes in technique or technology can have a substantial effect on outcomes, as shown by recent research relating to metal-on-metal hip devices.

Measuring adherence regarding intervention delivery has been rare in surgical trials, but can help in interpreting the applicability (generalisability) of the results. Example measures include specimen margin examination or node counts in cancer procedures, or taking photographs after completion of key parts of the procedure. Deciding on restrictions requires careful consideration of the research question and the potential risk of bias and confounders (such as associated treatments), although as few restrictions as possible is preferable.

### Who should deliver the intervention?

Every operation should be carried out or supervised closely by someone with appropriate level of expertise and training. Collectively, participating surgeons should have sufficient expertise in order for the surgical community to embrace the trial and its findings. The traditional approach—where each surgeon delivers both or all surgical interventions in the trial—has been criticised. A comparison could be deemed unfair if surgeons have more expertise in one intervention than another.

This problem can be managed in two ways. Firstly, trial participation can be restricted to surgeons with an acceptable level of expertise in both or all surgical interventions. Surgeon eligibility criteria have generally focussed on markers of training and previous experience of the intervention (for example, completing 10 laparoscopic hernia procedures). Professional grade, year of experience, and annual caseload can be used as markers, although a more rigorous standard of direct demonstration of surgical competency has also been proposed (for example, providing training and supervision before participation). Under the second approach, participating surgeons deliver only the interventions in which they have expertise (an expertise based trial). There is limited evidence about how well this approach works to date, and such designs are not without statistical and practical disadvantages. Whatever approach is adopted, other factors can lead to differences in outcome between surgeons (such as ancillary care and centre admission policies) although they are rarely, if ever, fully standardised.

### Impact of treatment preferences

The preferences of both patients and surgeons are a key factor that affects the success of a randomised controlled trial, and can be the decisive influence upon recruitment. If patients tend to prefer one of the treatments, they are unlikely to agree to be randomised in case they are assigned to another treatment. The merit of an otherwise well designed and conducted trial can be fatally undermined if too few surgeons are willing to be involved. There is, however, a strong relationship between the patient and the surgeon, who may have his or her own strong preferences and have traditionally acted as gatekeeper and...
Alternative devices with a larger head size and different bearing surface materials (such as metal-on-metal devices) have increasingly been used to reduce revisions. Total hip replacement is widely undertaken although revision is sometimes necessary, particularly in younger recipients. Operations involving different types of devices (varying bearing surface and head size) (n=402 051) were linked to revision operations.

Primary stemmed operations of total hip replacement done between 2003 and 2011

Findings

Metal-on-metal devices had poorer survival than devices with alternative surfaces.

Long term evaluation of procedures

Well designed, large observational studies (for example, based on registries) can be used to evaluate procedures in the long term study stage; they can also provide data for outcomes in subgroups of interest as well as rare endpoints in safety and effectiveness. From an assessment perspective, some national or nationally representative patient registries can be defined as observational studies collecting “uniform data, to evaluate specified outcomes for a population defined by a particular disease, condition, or exposure.” Registries can be designed to capture data for specific conditions or exposures (such as surgery or devices), types of healthcare service delivered (such as surgical treatment or diagnostic procedure), or specific outcomes (such as an adverse event, disorder, or disease), to improve the delivery of care.

Practical factors often determine which data are collected, but in principle, disease based registries have the advantage of enabling consideration of selection for a procedure and potential for associated bias in an evaluation. Procedure registries can provide useful comparative evidence for different interventions and devices. Long-standing procedure registries include those developed by professional societies such as the United Kingdom’s Society for Cardiothoracic Surgery’s adult cardiac surgery database or the Society of Thoracic Surgeons’ registry.

Other studies (including randomised controlled trials) can be nested in them. The Swedish national registry of gallstone surgery and endoscopic retrograde cholangiopancreatography (GallRiks) enabled a large cohort study to quantify survival and incidence of bile duct injuries and explore the relation between them.

The choice of surgical procedure or medical device can often vary greatly, even for similar patients within and between centres. For example, the figure shows the proportion of operations using abdominal access (versus thoracic access) in haïtal hernia repair, in hospitals in the Nationwide Inpatient Sample. The choice of access route was strongly influenced by surgeon practice and institutional culture, and was unlikely to be related to the hernia location for many hospitals. In most hospitals, the majority of hernia repairs were conducted via abdominal access—that is, the hernia location did not dictate the approach and therefore any confounding by indication will probably be limited. Identifying such practice and surgeon patterns can, therefore, help clarify the extent to which selection of patients for receiving the procedure (or device) may have occurred. Exploration of variations in practice can improve the design of comparative studies, by providing insight regarding the likelihood of the main potential bias—confounding by indication.

The modes of follow-up are critical, as are completeness and accuracy of data collection, which can lead to loss of follow-up and various misclassification biases (for example, outcomes of difficult operative cases being att-
Access route (% of abdominal repairs)

- Blue=percentage of operations with abdominal route; black=95% exact (binomial) confidence intervals. Use of the abdominal route varied from 0% to 100% across hospitals.

**SUMMARY POINTS**

- Rigorous evaluation of surgical innovations is needed in the assessment and long term study stages, which together meet the need for comprehensive outcome assessment.
- Randomised trials of surgical interventions, along with observational studies in the long term study stage, should be designed which acknowledge the complexity of surgery.
- Key issues for surgical trial design are specification of the interventions, who will deliver the interventions, and assessing the potential impact of patient and surgeon preferences.
- Long-term evaluations of the procedure and any related devices is needed, along with the development of data collection and methodology for surveillance.

**Surveillance of devices**

In the US and UK, manufacturers and importers are required to submit reports of device related deaths, serious injuries, and malfunctions to the regulatory bodies. US hospitals and nursing homes are required to submit reports of device related deaths and serious injuries to the manufacturer and only deaths to the FDA, but healthcare providers and consumers can submit reports voluntarily (through MedWatch). Such passive reporting systems typically have important weaknesses, including:

- Incomplete or inaccurate data that are usually not independently verified
- Data reflecting reporting biases driven by event severity or uniqueness, publicity, or litigation
- Causality cannot be inferred from any individual report
- Events are generally under-reported and this, in combination with lack of denominator (exposure) data, precludes determination of event incidence or prevalence.

However, reports received through passive and enhanced systems are often useful and have resulted in important public health alerts related to:

- Transvaginal placement of surgical mesh
- Use of recombinant bone morphogenetic protein in cervical spine fusion
- Interactions induced by magnetic resonance imaging in patients with implanted neurological stimulators.

In addition, the FDA has developed an enhanced surveillance system using several different modes of surveillance, including active surveillance. This system, known as the Medical Product Safety Network, provides national surveillance of medical devices based on a representative subset of user facilities. Routine data collection and monitoring for devices need improvement. Finally, when resources are available, active surveillance based on registries can also help monitor high risk surgery and devices, such as a national registry of implanted ventricular assisted devices.

**Summary**

A large, multicentre, randomised controlled trial in the assessment stage complements observational evaluation in the long term study stage. Large and preferably national patient registries are best suited for long term surveillance studies of surgical procedures. Surveillance of devices with improved data collection is needed.
Owing to the inherent complexity of surgery and variation in practice, both randomised controlled trials and surveillance studies face particular challenges. However, solutions are often available, and such difficulties should not prevent rigorous and comprehensive evaluation of surgical innovations.

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