



Will registries slow down or accelerate innovation?

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■ The increasing use of regional and national registries of surgical implants has raised concerns that the cost and consequences of these initiatives will adversely influence innovation. The opposite appears to be true, with no evidence of a reduction in overall innovation and an association of increased innovation in countries with more evaluation using registries.

Keywords: evaluate; innovation; joint registry

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Introduction

Surgical registries provide an observational assessment of either surgical techniques or, more commonly, surgical implants and have become increasingly commonly used over the past 20–30 years. Observational studies are generally ranked lower than experimental studies in the hierarchy of evidence. However, they do have several potential advantages over randomized controlled trials including lower cost, quicker results and involvement of a more representative, or real-world, population of patients. The disadvantages of registries include an inherent tendency to bias and confounding, which makes it difficult to compare different surgical techniques or different implants. Generally speaking observational studies and registries are best used to identify risk factors and prognostic indicators in circumstances where randomized controlled trials would either be unethical or impossible to undertake. Comparisons made in the 1970s and 1980s between observational studies and randomized trials demonstrated that observational studies often inflate positive treatment effects compared to randomized studies.^{1,2} In 2015, David Sackett, one of the founders of evidence-based medicine, described four worries regarding the quality of clinical evidence.³

- That clinicians might preferentially give new treatments to patients with better prognosis.
- That compliant patients might have better prognosis regardless of their treatment.

- That patients who liked their treatment might report better outcomes unrelated to the true efficacy of their treatment.
- That clinicians who liked the treatment might report spuriously better outcomes among patients who received them.

The basis of all of these worries is the issue of bias, and how failure to address it might produce spurious or incorrect conclusions. These concerns have become more of an issue as the use of surgical techniques and technologies has evolved and developed, particularly over the last 25 years. To counter this concern, more recent studies have shown little evidence that estimates of treatment effects in observational studies were larger or qualitatively different from those in randomized controlled trials.^{4,5}

There is no doubt that surgical techniques have dramatically changed patient care and, in the case of high-risk surgery, there is clear evidence of improvement in patient outcomes and reduction in operative mortality.⁶ But some surgical innovations have proved over time to have little value or to sometimes be harmful. For example, the use of internal mammary artery ligation was shown to be ineffective as a treatment for angina.⁷ More recently the ORBITA study, which was the first trial in over 40 years to compare revascularization of the coronary arteries with a placebo intervention, showed no advantage of stenting in patients with stable angina.⁸ Another example is the CSAW trial, which investigated the treatment effect of one of the most commonly performed arthroscopic procedures in orthopaedics: subacromial decompression. The surgical treatment had first been introduced in the early 1970s but had never been rigorously investigated in a randomized controlled trial. This trial also used a placebo intervention control and found no difference in outcome for the two surgical groups, raising significant concerns regarding its continued use.⁹

Existing hip and knee replacement registries in Europe

European registries began with the Swedish Knee Arthroplasty Register founded in 1975 and the Swedish Hip

Arthroplasty Register founded in 1979. Other Scandinavian countries then introduced registries during the 1980s and 1990s with more widespread use of registries occurring after the year 2000. These registries have had an important effect on the long-term outcomes of joint replacements.¹⁰ In order to assess the overall size and scale of joint replacement registries Lubbeke et al undertook a mapping exercise of existing hip and knee replacement registries in Europe.¹¹ They identified 24 registries, most of which had national coverage. These registries covered between them 3.1 million primary total hip replacement records and 2.5 million primary total knee replacement records. The principal assessment of the joint replacements was lifespan and the occurrence of revision surgery. Other joint replacement registries exist in North America, Australia and New Zealand. Some registries also assess quality of surgical and perioperative care and hospital performance. There is an increasing emphasis on harmonization of registry datasets and the ability to merge data from these different sources to add power to predictive studies and to improve outcomes for patients. Overall, coverage is extremely high, with more than 95% of all joints replaced being included in countries with active registries. National and international benchmarking is becoming a much greater focus of attention of the registries and in the United Kingdom and in Australia there is active work to identify implant outliers which may benefit from attention. Reviews of the impact of registries suggest that the overall influence is positive in terms of healthcare processes and outcomes. It is proposed that the introduction of surgical registries such as hip prosthesis registries in countries currently without registries would result in significant cost savings.^{12,13}

Problems with surgical implants (outliers) and the role of regulation

Osteoarthritis of the hip has generally been treated very successfully with total hip replacement surgery. In 2005, a new design was introduced in which metal bearings were used with the claim that they would improve the life span of the implant and that, because of the size of the bearings' surfaces, there would be a reduction in the risk of dislocation which would be particularly advantageous in younger patients. Unfortunately, this new concept and design was not rigorously tested prior to widespread adoption and use. One particular metal-on-metal design was manufactured by Depuy (Johnson & Johnson) as the ASR XL acetabular system. The ASR hip was approved by the Food and Drug Administration (FDA) through its 510(k) process. This process was introduced in 1976 as part of the medical device amendments to the Federal Food, Drug and Cosmetic Act. Through this route new innovations and devices can be approved on the basis

that they are 'substantially equivalent' to a device that is already on the market; what is known as a 'predicate'. In these circumstances data regarding safety and efficacy are not required. Unfortunately, over a period of 5 to 10 years after its introduction it became clear that the device had a fundamental flaw in its design. There was tendency to wear particle production at the metal-on-metal interface. This was first recognized in a presentation at the British Hip Society, which showed that 21% of this type of design of hip had to be revised at four years after implantation and that this had risen to 49% at six years.¹⁴ Cases such as the metal-on-metal hip replacement have driven a greater consideration and inspection of the best way to introduce and adopt novel surgical innovations. There is, on the face of it, no reason why evidence-based principles should not be used for surgical innovations as they are for the introduction of drugs or pharmaceuticals. A review of primary hip replacements showed that 261 hip implants were available in the United Kingdom, with only 20% supported by good evidence.¹⁵ In a further piece of work looking at the evidence for new hip and knee replacements no evidence was found that new implants offer any benefits over existing ones.¹⁶ The issues related to metal-on-metal hip replacements are not the only example of problems with medical devices. Transvaginal mesh products have been used for pelvic organ prolapse over the last 20 to 30 years. These devices were introduced on the basis of weak evidence and approved by regulatory authorities in both North America and Europe. Concerns have been raised about the safety of transvaginal meshes.^{17,18} A review of the regulatory ancestry of all surgical meshes performed reveals that all surgical meshes currently on the market have been approved via the 510(k) route.¹⁹ As a consequence of these concerns the Food and Drug Administration reclassified these devices in January of 2016 requiring the much more stringent pre-market approval process for their use. Another consequence of the relative ease of approval of novel devices and implants is that manufacturers are tempted to introduce multiple new implants onto the market, often without good evidence, in the hope of gaining market share rather than necessarily expecting significant disruptive innovation.

Structure of the implant industry

A further concern is the structure of the implant industry, which when all medical devices and technologies are considered is as large as the pharmaceutical industry, in terms of healthcare expenditure. Despite its size, the structure of the medical device industry is quite different. Many more medical devices than drugs are under development at any given time. The amount of funding available for these devices is proportionately much smaller than is the case

for pharmaceuticals. The principal concern is that the structure of the industry business model does not include the same allocation of funding for evaluation and pre-marketing clinical trials as is the case for drugs. This behaviour of the medical device industry is linked to two things: the first is professional decision making and the second is regulations.

Surgical decision making

The decision to use and adopt a surgical innovation is often made by an individual surgeon or by small groups of surgeons who might discuss new innovations at subspecialty conferences or meetings. The innovation is introduced to the surgeon by representatives or members of the manufacturing industry who will attempt to persuade the surgeon on the basis of pre-clinical evidence both in vitro and in vivo that the new innovation may have advantages for patient care. The master/student model of teaching and training of surgeons has evolved since the middle ages, where surgeons are taught by expert surgeons who have learnt their craft and skill over a lifetime. The student observes the master and emulates and replicates their techniques and decision-making approaches. It is possible for widespread use of novel innovations to occur on the basis of professional decision making without there being substantial and robust evidence. Theories regarding the influences on adoption of novel technologies abound and include the unified theory of acceptance and use of technology.²⁰ Some studies suggest that between 30% and 40% of patients do not receive care that is based on best scientific evidence and a staggering 20% to 25% of patients may receive care that is potentially harmful.²¹

Attempts have been made to improve the evaluation of novel surgical innovation. This includes the IDEAL framework (innovation, development, exploration, assessment and long-term framework).²² In this framework an innovation is described as a new or modified surgical procedure that differs from currently accepted local practice, the outcomes of which have not been described and which may entail risk to the patient. The IDEAL framework also describes the adoption of an innovation as 'the increase in the number of overall surgeons doing the procedure over time, which will occur until it is either accepted by surgeons or discarded'.

Changes to the regulation of surgical implants

As a consequence of situations such as those encountered with metal-on-metal hip replacements and vaginal meshes, regulatory changes are underway. Changes were introduced both in North America and in Europe in 2017 and will influence the evaluation of medical devices. In the United States the 510(k) route remains the most common regulatory pathway used by manufacturers. It

requires evidence of substantial equivalence and does not generally require any clinical data prior to marketing. The route to market is, as a consequence, substantially quicker and much less costly than pre-market approval, which is the alternative and generally restricted to high-risk implants and devices. Analysis of FDA databases between 2015 and 2017 has revealed that 97.9% of submissions to the FDA were via the 510(k) route, 0.8% were for de novo devices and 1.4% were applications through pre-market approval. For orthopaedics in particular, 99.4% of applications were via the 510(k) route and 0.6% were via pre-market approval.²³ It is estimated that changing from 510(k) approval to pre-market approval triples development costs for the average orthopaedic implant or device. There are competing concerns here. The first that a lack of evidence for a given device or a given class of device may be putting patients at unnecessary and arguably unacceptable risk, where clinical evidence on safety and efficacy has not been appropriately collected. The argument against this is that if a significant change is made to the regulatory pathways for medical devices and surgical implants the industry will not be able to cope, its current business models will fail and that large sections of the industry will become non-viable, resulting in bankruptcies and redundancies of large numbers of staff employed in this sector. It is clear that there is a strong industry lobby to reduce or diminish regulation of surgical devices. On 20 July 2011 the US House Energy and Commerce sub-committee on oversight and investigations held a hearing on 'medical device regulation: impact on American patients' innovation and jobs'. Congressman Chris Starns was the sub-committee chairman and he argued strongly that the FDA's regulation of medical devices was too burdensome and that it stifled innovation and drove some manufacturers overseas.²³ The FDA in the United States is moving away from the use of randomized trials to the increased use of post-market surveillance and intends to fortify the 510(k) system. This falls significantly short of the Institute of Medicine's recommendation to eliminate the 510(k) route. The US system will improve device recall and will introduce new procedures for reviewing existing devices.

On the 26 May 2020 the new EU Regulation for Medical Devices (MDU, (EU) 2017/45) will come fully into force. It is claimed that this is a fundamental revision and will 'ensure a high level of safety whilst supporting innovation'.²⁴ In Europe, the requirements have significantly tightened, all implants will now have to be identified by a unique identifier code and this will be registered on a database (EUDAMED). Notified bodies will still grant marks of conformity (CE marks) but there will be increased scrutiny of notified bodies. The notified bodies will require increased clinical evidence and a routine post-market surveillance plan. There will also be a need for serious

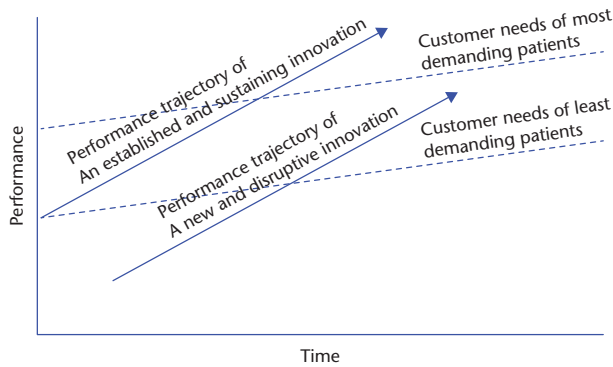


Fig. 1a Showing performance trajectories over time of established and sustaining innovations. The area between the dashed lines represents the gap between the least and most demanding patients. The pace of change of established innovation is nearly always greater than the capacity of patients to take it on board. This allows the potential for new disruptive technologies to find a place in the market. Currently, in joint replacement surgery, the industry and professional focus is predominantly centred on sustaining innovations due to financial, organizational and professional incentives.

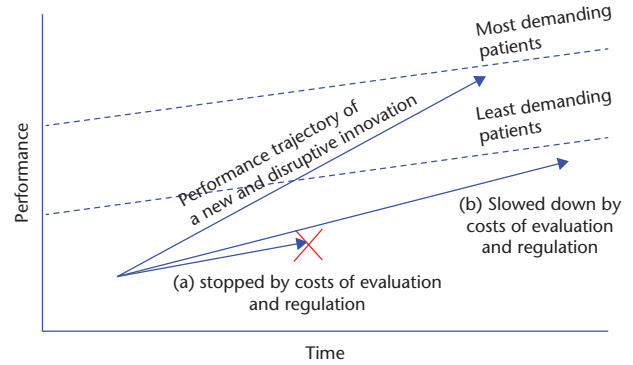


Fig. 1c Showing performance trajectories over time of a new and disruptive technology. Including examples of innovations that have either been (a) stopped, or (b) slowed down by the costs and difficulties of increased regulation and evaluation. Adapted from Christensen CM, Bohmer RMJ, Kenagy J. Will disruptive innovations cure health care? *Harvard Business Review* 2000;September–October:102–117.

drivers of the need for more evidence of benefit and potential harm to patients.

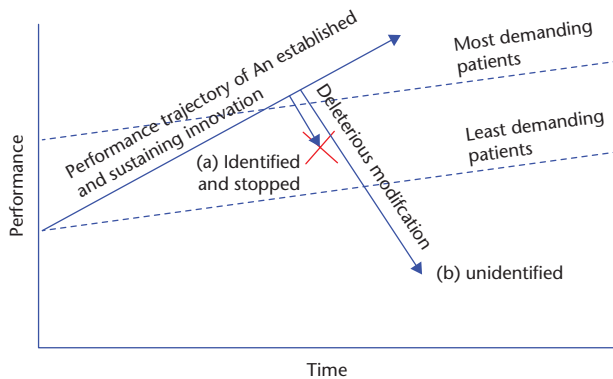


Fig. 1b Showing performance trajectories over time of established and sustaining innovations where a deleterious modification has been (a) identified early and stopped by an effective surveillance programme and registry, or (b) left unchecked in the absence of clinical evidence.

incident reporting. This incident reporting may allow early detection of problems such as those encountered with metal-on-metal hips. The notified bodies will be audited by competent authorities, who will have access to the EUDAMED database, which will allow clinical investigation data to be compiled with vigilance reports. The European system is also likely to require high-risk implants to undergo a much more rigorous assessment by the European Medicines Agency, which is the regulator for pharmaceuticals. These changes to the regulation of medical devices including surgical implants are key

Disruptive surgical innovations

Christensen wrote in his book *The inventor's dilemma* that disruptive innovations should be 'cheaper, simpler, more convenient products or services that start by meeting the needs of less demanding customers'.²⁵ Christensen is of the belief that the traditionally dominant businesses in a given market will have focussed on the needs of more sophisticated and wealthy customers. As time passes simpler products get better and, although technologically inferior, gain significant market share by addressing the needs of the vast majority of customers (Fig. 1). Arguably the major focus at present in the field of orthopaedic implants and joint replacement surgery is on established and sustaining innovations rather than novel or disruptive innovation. This is due to structural or organizational factors and financial incentives spanning health delivery and the medical device industry. The theoretical advantage of introducing improved evaluation of patient outcomes through approaches such as surveillance and registries is that iterative modifications to existing technology that turn out to be less effective or more harmful than the existing technology are quickly identified and overall harm is reduced (Fig. 1). The concern is that the costs and overall burden of increased regulation and the requirement for clinical evidence will either slow down or stop new disruptive innovations. If innovation occurs without regulation and monitoring, either from the regulatory authorities or from the professional



Fig. 2 The European Commission Regional Innovation Scoreboard which classifies regions of Europe into four groups: Innovation Leaders, Strong Innovators, Moderate Innovators and Modest Innovators. The most innovative regions are in Sweden, Denmark, Finland, Germany and the UK, all of which have established Joint Replacement Registries. https://ec.europa.eu/growth/industry/innovation/facts-figures/regional_en (last accessed 30 September 2018).

bodies involved, then patients may, and probably will in some instances, come to harm.

European Commission Regional Innovation Scoreboard (RIS)

Innovation is crucial to the economic success of any country. In order to assess innovation, the European Commission has implemented a Regional Innovation Scoreboard. This assesses the innovation performance of European regions for a limited number of indicators. The

RIS 27 covers 220 regions across 22 European Union countries and Norway, Serbia and Switzerland. In addition to this Cyprus, Estonia, Latvia, Lithuania, Luxemburg and Malta are included at country level. The RIS contains a detailed breakdown of performance. The scoreboard published in 2017 shows that the most innovative regions are overall located in the most innovative countries. The most innovative region in the European Union is Stockholm in Sweden, followed by Copenhagen in Denmark and the southeast of England (Oxford, Cambridge and London in the United Kingdom) (Fig. 2). What is interesting is that the countries with most innovation overall are countries with long established joint replacement registries, which are in Sweden, Finland, Norway, Denmark, the Netherlands and the United Kingdom (Fig. 3). From this evidence, it does not appear that the existence of national joint replacement registries impairs innovation in that country. Indeed, the opposite would seem to be true. This apparent association requires further inspection and research.

Summary

The widespread use of registries for monitoring of selected orthopaedic implants and techniques is generally welcome. There is evidence over successive years that improvements are occurring in the safety and performance of most surgical implants. This exceptional performance of modern hip and knee replacements means that new innovations have a real challenge if they are to genuinely improve outcomes for patients. There is an imperative to properly assess new innovations and both prove benefit and also demonstrate that there is no harm associated with their use. There is no evidence that the use of registries has reduced innovation in hip and knee replacement surgery, indeed there continues to be a proliferation of new designs and new technologies in this area. Innovation is particularly strong in countries with functioning national registries. There remains doubt as to whether or not registries are sufficiently free of bias to allow comparisons to be made between implants but embedding randomized trials within registry infrastructures may be a cost-effective way of addressing specific questions. There is a need for progressive and careful tightening of the regulatory framework for implants, and this is occurring. It will be interesting to see whether the regulatory approach taken by the European authorities differs in its effectiveness from the approach taken by the Food and Drug Administration in the United States. A significant responsibility rests with the surgical profession and improvements need to occur in training and education about how best to determine the true effectiveness of innovations.



Fig. 3 Showing countries in Europe which have active hip and knee replacement registries. The registries are sub-divided into those with more than and less than 75% national coverage.

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