Volume 12 • Number 4 • 2009
VALUE IN HEALTH

Economic Evaluation for Devices and Drugs—Same or Different?

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Introduction

Although the general methods of economic evaluation are well established [1,2], it is often their detailed application that raises methodological challenges. Most international guidelines for economic evaluation, although appearing to be generic, have been written with pharmaceuticals in mind [3]. For example, they typically assume that randomized controlled trials (RCTs) will be available for the assessment of relative treatment effect. In this article, we argue that the economic evaluation of devices raises additional challenges that international guidelines frequently overlook.

Six Reasons Why Devices Are Different

The first reason is the rather obvious one that many devices are diagnostic. This raises two challenges, the first being that the value of improved diagnosis cannot be separated from the value of the improvement in patient outcome resulting from the subsequent treatment. This problem is not insurmountable, but makes the economic evaluation of some devices much more complicated.

A further challenge in the evaluation of diagnostic devices is that they often have multiple applications (e.g., a positron emission tomograpahy scanner). Although this is not unlike the problem that drugs often have multiple indications, the device is indivisible, which means that the overall value of the device is some weighted average of its use in multiple applications. On the other hand, being divisible, the value of a drug can be assessed in each indication, and a judgment reached on each separately.

The second way in which devices are different is in the difficulties in undertaking RCTs. By the time a drug reaches phase III of clinical development, its dosage and route of administration will typically be set. Therefore, although it is well known that the efficacy demonstrated in RCTs does not always translate into practice, the results from trials provide a reasonable basis for conducting an economic evaluation.

On the other hand, devices frequently undergo product modifications, some of which may impact on efficacy. In addition, there is often a "learning curve" associated with the use of a device, particularly those used in surgery. Therefore, an RCT comparing a traditional surgical procedure with a new one involving a device could well be demonstrating the difference between experience with the old procedure versus inexperience with the new, rather than differences between the procedures themselves. This issue was evident in the Conventional versus Laparascopic-Assisted Surgery In Patients with Colorectal Cancer (CLASICC) trial for laparoscopic colorectal surgery, where outcomes in the laparoscopic arm were seen to improve over time as the surgeons gained experience with the new technique [4].

All of this means that there is unlikely to be a substantial "steady-state" period, during which the device could be evaluated in an RCT. Therefore, it might be better to view the clinical and economic evaluation of devices as an iterative approach, with revisions being made to the estimates as more evidence is gathered on effectiveness in actual use.

In addition, it is sometimes more difficult to undertake blinded studies with devices, with the risk that biases can be introduced. For example, blinding can be difficult (indeed unethical) if the alternative would have to be a sham procedure. Also, patients are sometimes reluctant to enter RCTs if they are concerned about being randomized to an invasive surgical procedure, as opposed to a minimally invasive one.

The third reason why devices are different has already been touched upon. Namely, the efficacy of a device depends not only on the device itself, but how it is used. Again, this is particularly true for devices used in surgery, as the clinical outcome can depend on the skill or experience of the surgeon. On the other hand, drugs are a classic case of an "embodied technology." That is, as long as the drug is given in the right dose, the efficacy relates solely to the drug itself, not the person administering it.

The need to adjust for user characteristics further complicates the design of RCTs and user performance is a potential confounder in the analysis of observational data on the efficacy of devices. Indeed, it might be preferable to undertake more multicenter studies than is typical for all but the large phase III studies of drugs. Whether these studies are randomized or not, the statistical analysis would be more complicated, because it would need to allow for treatment center effects. Taken in conjunction with the points made above, it is clear that the design and analysis of clinical studies of devices can be more challenging than comparable studies of drugs.

The fourth way in which devices are different from drugs is that implementation of a new therapy involving a device can have wider economic implications. For example, there may be a need for training, or more fundamentally, the local organizational context may be important for harnessing the improved cost-effectiveness of a device. In the technology assessment report for the National Institute for Health and Clinical Excellence (NICE) on stapled hemorrhoidopexy, the authors noted that the cost-effectiveness of the staple gun was likely to dependent on the potential, in each location, to switch more patients to day case surgery [5]. Such organizational adjustments are rarely examined in economic evaluations. They can also be important in the case of drugs (e.g., a new drug that increases potential for early discharge from intensive care) [6], but are much less common.

The fifth way in which devices are different from drugs is that equivalent clinical evidence may not be available for all products, making comparisons difficult. Those undertaking economic evaluations are often quick to "genericize" their recommendations,

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10.1111/j.1524-4733.2008.00476.x

1098-3015/09/402 402–406

unless there is specific evidence to differentiate products. This position is possibly driven from experience with pharmaceuticals, where there is clinical evidence on each product, and where assumptions about class effects are common, unless there is specific head-to-head trial evidence to the contrary. In addition, there are now acceptable methods for making indirect or mixed treatment comparisons, providing sufficient clinical data are available [7].

Class effect recommendations can also be made for medical devices, but can sometimes be flawed, or based on inadequate evidence. For example, in 2003–2004 NICE issued positive guidance through its technology appraisal program for Gynecare-TVT (tension-free vaginal tape; a suburethral sling for stress urinary incontinence) [8], and three branded devices for use as second-generation endometrial-ablation technologies for heavy menstrual bleeding [9]. Although there were not major differences in cost-effectiveness between the various devices, the technology appraisals did demonstrate differences in outcome that may be important to some patients.

Nevertheless, when these treatments were incorporated into NICE clinical guidelines in 2007 [10,11], the recommendations for both slings and second-generation ablation technologies were based on the assumption of a "class effect." Both markets now have many entrants, but little detailed review of the evidence for each available device has been undertaken, to establish whether there are important differences in clinical or cost-effectiveness.

Although approving new market entrants as quickly as possible may appear attractive as a method of increasing competition and therefore reducing costs to the provider, the practice may be short sighted. At a minimum, it is a disincentive for manufacturers to invest in research. This is in contrast to pharmaceuticals, where evidence on efficacy and safety is legally required for every product. The incentive in the devices field is to be a fast follower and avoid the high costs of research attached to being first to market. Trials to demonstrate the role of devices in clinical practice and longer term effectiveness are often over and above what is needed to achieve a device Conformité Européene (CE) mark, the requirement for market authorization in the European Union. Extrapolating evidence from one device to another may appear attractive in the short term, but this lower hurdle for later market entrants could also impact patient safety, as the longer-term follow-up data generated from the evidence-base for one product may well not be attributable to all. Different devices, though having the same clinical indication or outcome, may have different physical properties, or even modes or action, which should not be considered generic without adequate supporting evidence.

The sixth way in which devices are different from drugs is that prices are much more likely to change over time because of the market entry of new products, or because of the ways in which procurement takes place in many health-care systems. On the other hand, in many countries, once the price of a drug is negotiated, it is more likely to stay at or near that level until the patent expires.

Indeed, because medical devices are often procured through different mechanisms, more aligned with commodity products than pharmaceuticals, the outcome of an economic evaluation and health-care guidance based on formal technology appraisals can directly influence pricing in the market place. For example, if a technology assessment determines that clinical practice should change to implement a new technology, it is also determining the "old" technology is now obsolete, at least in that given population. Then, because of the way medical devices are procured, the price for the "obsolete" technology is rapidly driven down to help create head room to fund the new "approved" technology. If the price of the obsolete technology falls faster than the price of the new technology, then the cost difference will increase, changing the implied incremental cost-effectiveness ratio. This could potentially change the decision, if this is based on a cost-effectiveness threshold.

This issue arose in the recent reappraisal of drug-eluting stents by NICE. The Appraisal Committee recognized that the clinical effectiveness had not changed since the original guidance was published [12], but noted the greater fall in bare metal stent prices (as compared with those for drug-eluting stents) since the original guidance. Increasing the incremental cost while not changing the incremental effectiveness increased the incremental cost-effectiveness ratio (ICER) to a level deemed not to be cost-effective. Therefore, in the Appraisal Consultation Document, the Committee recommended against the use of drug-eluting stents [13]. This decision has subsequently been reversed in the Final Appraisal Determination, though at the time of writing, this has yet to be confirmed as final guidance to the NHS.

Of course, there are health-care markets (most notably the United States) where special deals are negotiated for drugs and where rebates are offered. In these markets, and more generally for devices, an incremental cost-effectiveness ratio generated in a single economic evaluation may not be very generalizable, as prices are not stable over time or between locations.

Conclusions

Although the methods of economic evaluation can be equally applied to drugs and devices *in general*, we have identified several *specific* methodological issues that require more attention if reliable and informative evaluations of devices are to be conducted.

The views expressed are those of the authors themselves and are not necessarily shared by their employing organizations.

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Assessing the Clinical and Cost-Effectiveness of Medical Devices and Drugs: Are They That Different?

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Introduction

The term "medical device" covers a wide range of technology. According to the European Union (EU) directive 2007/47/EC, a "medical device" is defined as "any instrument, apparatus, appliance, software, material or other article, whether used alone or in combination, including the software intended by its manufacturer to be used specifically for diagnostic and/or therapeutic purposes and necessary for its proper application, intended by the manufacturer to be used for human beings for the purpose of diagnosis, prevention, monitoring, treatment or alleviation of disease" [1]. Although medical devices and drugs both aim at restoring or improving health, they are substantially different in their mode of action. While drugs interact with biochemical pathways in the human body, devices make use of a great diversity of actions and reactions (e.g., radiation, heat, mechanical, electrical). In addition, devices may be used for both diagnostic and therapeutic purposes. Thus, one may conclude that devices are fundamentally different from drugs in nature and by definition.

The goal of health technology assessment (HTA) is to assess the clinical and cost-effectiveness of existing and emerging therapies—be those drugs or medical devices, or any other form of medical technology—to inform the policy decisions of healthcare decision-makers on therapy access [2]. HTA is a two-stage iterative process. First, a scientific *assessment* of the (clinical and economic) evidence for a health technology is undertaken. Then, based on this assessment, an *appraisal* of the evidence (together with consideration of political, social, ethical factors) is made, and a policy decision made, e.g., whether to fund or not to fund the therapy in question. Increasingly, governments across the world are mandating agencies such as the National Institute for Health and Clinical Excellence (NICE) to issue national policy guidelines on the use of drugs and medical devices based on such a system of HTA and evidence-based appraisal.

Do the conceptual differences in drugs and medical devices require a different framework of HTA or evidence-based appraisal? In this article, we argue that although there are important differences that need to be taken into account when assessing the clinical and economic evidence base for medical devices—1) the medical device licensing process; 2) the device-operator interaction; and 3) the incremental innovation of medical devices—these should not be seen as an obstacle to producing a robust evidence base on the clinical and cost-effectiveness of medical devices.

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Medical Device Licensing

Drug licensing and market access approval by the Food and Drug Administration (FDA) and international equivalents, such the European Medicines Agency (EMEA) in Europe, require manufacturers to undertake randomized controlled ("phases II and III") trials to provide the regulator with robust evidence of their drug's efficacy and safety. Nevertheless, the evidence hurdle for licensing of medical devices is traditionally been much lower than for pharmaceutical products [3]. For high-risk devices or new devices for which there is no comparator product on the market (class III devices), the FDA require manufacturers to submit a premarket approval application, from which regulators determine whether there is sufficient evidence of safety and effectiveness for the intended uses [4]. In practice, this standard is often met by small clinical trials in select groups of patients. The studies often do not employ randomized designs, and the FDA generally does not require manufacturers to collect long-term efficacy data [5]. HTA agencies and payers are therefore often faced with the dilemma of assessing the clinical and cost-effectiveness of medical devices in the face of absence or lack of randomized controlled trial (RCT) evidence. For example, in two recent technology appraisals by NICE of cochlear implants and spinal cord stimulation for neuropathic back pain, manufacturers submitted to NICE an evidence base of one and two RCTs,

respectively. In contrast was the substantive body of nonrandomized evidence for each of these technologies (e.g., 72 case series for the use of spinal cord stimulation).

Variations in the evidence base available for devices implies that unlike with drugs, ascertaining the clinical and cost-effectiveness of medical devices will more often than not require the consideration and analysis of data from observational studies. This has direct implications regarding the level of sophistication of the statistical methods required to robustly address some of the issues commonly associated with observational data, such as selection bias and confounding factors. In the context of premarket evaluations of medical devices within the FDA's Center for Devices and Radiological Health, Bayesian methods for the analysis of trial data have been proposed as an alternative framework for evaluation [6]. The flexibility of these methods may make them particularly well suited to address many of the issues associated with the assessment of clinical and economic evidence on medical devices, such as learning effects, lack of head-to-head comparisons between different devices, variations in primary outcome measures, among others [7,8].

Device-Operator Interaction

The use of many medical devices, such as the two examples described above, involve an interaction between the device, a clinical procedure, and the clinician (or "operator"), where important improvements in technical performance of a new technique may occur over time—a "learning curve" effect [9,10]. During the learning curve, errors and adverse outcomes are more likely. This can distort the outcome results of a clinical trial if the analysis does not account for learning effects explicitly. For example, in Figure 1, a simulation is shown of comparison of the use of medical device involving a clinical procedure to the management of the same condition by a drug. If the comparison were to be conducted early in the experience of the clinician of the new medical device (time A), then it would be concluded that drug treatment performs better. Nevertheless, after a short period of time and with increasing clinician experience, their performance of the medical device increases markedly, such that by time B, the performance of the medical device is superior to the drug. There are few published examples of the use of medical devices where the learning curve has been characterized (e.g. laproscopic gastrectomy and inguinal hernia repair) [10]. Nevertheless, the potential interaction of a medical device and the operator needs to be recognized and not be underestimated in the HTA process.

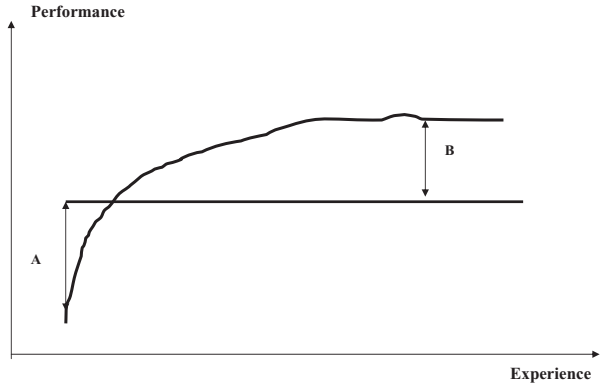

Figure 1 Hypothetical learning curves for medical device versus drug. Adapted from Ramsay et al. (2001) [7].

A variety of mathematical models—multilevel, latent curve, and time series—have used to explore potential learning effects on clinical and nonclinical data [10].

Incremental Innovation

Invariably, over the life of a medical device, incremental (sometimes stepwise) technological innovation takes place. For example, in the case of spinal cord simulation, the last 10 to 15 years have seen progressively miniaturized devices, with longer battery life, increasing number of electrode contacts with increasing sophistication and flexibility of choice in stimulation parameters and settings [11]. As a result, the level of patient benefit (pain relief) has steadily improved over time with the use of spinal cord stimulation. Although promoting an expedite entrance of innovative products into markets might be justified as a vehicle to enable individuals to benefit from advances on health technology at a faster pace, caution should be exerted to ensure patients' safety. Conditioning the licensing of innovative devices on the conduct of robust pragmatic RCTs or well-designed observational studies might help preventing cases such as that of the Sprint Fidelis implantable cardioverter-defibrillator lead, found in practice to be associated with an unexpectedly higher failure rate than that suggested on the basis of bench testing [12]. Furthermore, increasing the quality and size of the evidence based on effectiveness and cost-effectiveness of medical devices will facilitate the HTA process by allowing the exploration of the effectiveness of products within the same class.

Conclusions

We have highlighted that there are important differences between medical devices and drugs that impact on the assessment of their clinical and cost effectiveness. Nevertheless, as for drugs, quality of manufacturing, safety, effectiveness, and cost-effectiveness should be the four pillars underpinning the evaluation of medical devices. We have argued that the differences in drugs and medical devices have direct implications for trial design and statistical methods to be used for the collection and the statistical analysis of clinical and economic data on medical devices and also the assessment component of the HTA process. Nevertheless, we would also argue that the requirements for the policymaking (appraisal) component of the HTA process are no different for drugs and medial devices.

In HTA, health-care decision-makers and payers require a common metric from the HTA process to appraise the evidence for health-care technologies across different medical conditions. The cost per quality of life in many settings has become that gold standard metric, regardless of whether a policy maker is evaluating a drug, medical device, or any other health-care technology. HTA methods guidelines, including those of NICE and Canadian Agency for Drugs and Technologies in Health, currently provide no distinction in their approach to the scientific assessment of the evidence of clinical of drugs and devices [13,14]. An important future challenge for the HTA community is therefore to develop methods to incorporate consideration of medical device-specific issues, particularly the device-operator learning curve and incremental innovation in device over time, when assessing their clinical and cost-effectiveness.

An important recent development by the Centers for Medicare and Medicaid Services (CMS) in the United State has been the development of a "coverage with evidence development" policy [15]. If CMS determines that the information necessary for a coverage determination is not available, Medicare will reimburse new medical devices only if patients enroll in clinical trials

supported by the developers of the technologies or other related groups. With these data, payers are better positioned to make evidence-based determinations of whether new devices are "reasonable and necessary." This policy has stimulated a number of pragmatic real-world RCTs for medical devices. Such conditional decisions are being used in other setting. For example, returning to the example of spinal cord stimulation, NICE have recently announced an "only in research" recommendation for the use of the device in patients with refractory angina and chronic limb ischemia [16].

Is the HTA process for medical devices and drugs that different? As has been argued here, differences in the nature of medical devices and drugs (notably the operator-device learning curve and incremental device innovation) do require the HTA community to reflect on whether their current assessment methods adequately take account of the specific features of medical devices. In the meantime, and in the face of current and likely future trends in licensing, "coverage with evidence" or "only in research" policies, is an important output of HTA appraisals of medical devices to incentivize the industry to collect the necessary standard of evidence to appropriately assess their clinical and cost effectiveness.

Conflicts of interest: Rod S. Taylor is paid consultant for Medtronic International a medical device manufacturer and is a member of the NICE Appraisal Committee.

Cynthia P. Iglesias is currently receiving a Health Services Research and Health of the Public Fellowship funded by the UK Medical Research Council.

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