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World Health Organization

MEDICAL DEVICES: MANAGING THE MISMATCH

An outcome of the Priority Medical Devices project

Clinical evidence for medical devices: regulatory processes focussing on Europe and the United States of America

Background Paper 3

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Contents

Preface

In 2007, at the request of the Government of the Netherlands, the World Health Organization launched the *Priority Medical Devices (PMD)* project to determine whether medical devices currently on the global market are meeting the needs of health-care providers and patients throughout the world and, if not, to propose remedial action based on sound research.

The project gathered the information required by conducting literature reviews and surveys, and by convening meetings of specialist consultants.

The project addressed various complementary issues:

- the global burdens of disease and disability;
- guidelines on clinical procedures for the management of diseases and disabilities;
- projections of future burdens of disease and disability in the context of demographic trends;
- cross-cutting issues, such as the training of medical device users, medical device design, contextual appropriateness of medical devices, and regulatory oversight;
- catalysts of, and barriers to medical device innovation and research.

The original objective of the *PMD* project was to identify gaps in the availability of medical devices. The findings of the project showed that gaps in the availability of medical devices is not the primary issue, but rather a number of shortcomings spanning several facets of the medical device sphere. This result prompted a change of direction in which the project shifted its focus onto the many shortcomings related to medical devices.

These problems, challenges, and failures amount to a mismatch, rather than a gap, that prevents medical devices from achieving their full public health potential.

The *PMD* project also produced a report *Medical Devices: Managing the Mismatch* aimed at achieving two objectives: the first, to inform national health policy-makers, international organizations, manufacturers and other stakeholders of the factors preventing the current medical device community from achieving its full public health potential; the second, to provide a basis on which all players in the medical device scene can together use the findings and recommendations of the *PMD* project to make public health the central focus of their activities.

This paper is part of a series of documents produced as background material for the *PMD* project report. The following papers are available as part of this series:

1. A stepwise approach to identifying gaps in medical devices (Availability Matrix and survey methodology)
2. Building bridges between diseases, disabilities and assistive devices: linking the GBD, ICF and ISO 9999
3. Clinical evidence for medical devices: regulatory processes focussing on Europe and the United States of America
4. Increasing complexity of medical devices and consequences for training and outcome of care
5. Context dependency of medical devices
6. Barriers to innovation in the field of medical devices
7. Trends in medical technology and expected impact on public health
8. Future public health needs: commonalities and differences between high- and low-resource settings

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Introduction

Health-care providers, patients, organizations and nations are confronted daily with decisions about the appropriate use of medical devices. Whether it be a cardiologist choosing to implant a bare metal stent or a drug-eluting stent in a patient with newly diagnosed coronary disease; a general practitioner in a rural setting using one type of suture material over another, depending on their availability and cost; or a health system deciding what technologies to offer for colon cancer screening; medical devices are numerous, costly and indispensable to medical practice. Few physicians and patients understand what defines a medical device and the process by which medical devices are evaluated and approved for use.

This paper will review the process of pre-market evaluation and post-market surveillance of medical devices, and discuss the existing gaps in clinical evidence. It will examine the mechanisms in place in the United States of America and the European Union for review and approval of medical devices that permit their use in clinical practice. It will compare these processes and point out existing gaps in, and barriers to evidence based decision-making in both settings. The paper will end with recommendations about how all nations can improve the systems currently in place so as to take advantage of effective devices while limiting access to unsafe or ineffective technology.

Pre-market evaluation of medical devices

Historically, pre-market evaluation of medical devices has focused on both safety and effectiveness (or performance), although the emphasis in early phase clinical trials continues to be on safety for investigational devices. There is often tension between the level of clinical evidence required for approval, and concerns about limiting innovation of potentially breakthrough medical devices. To date, regulatory agencies have attempted to streamline clinical evidence requirements to address safety and effectiveness or performance questions raised during the pre-market review process.

The European Union

For the past 20 years, European nations have codified laws to promote the development and use of safe and effective medical devices. European Union (EU) regulation is built on trust in the stakeholders within the system. Requirements can be verified by Notified Bodies or Competent Authorities. In the 1990s, the European Commission, which is the legislative body of the EU, passed a set of three directives that regulate the sale of medical devices within the European Economic Area (EEA). These directives are binding in all EEA countries (and all countries must implement them into their legal systems); violators can be prosecuted. The three directives are:

- Directive 90/385/EEC – Active Implantable Medical Devices Directive (AIMDD)
- Directive 93/42/EEC – Medical Devices Directive (MDD)
- Directive 98/8/EC – In Vitro Diagnostic Directive (IVDD).

These three directives, in combination with six implementing directives (covering, among other topics, reclassifications of general medical devices and those derived from animal tissue), specify the terms under which more than 8000 types of medical devices can obtain a Conformité Européenne (CE), and thus be sold in the EEA, within the European free trade region and in some countries that have bilateral treaties with the EEA, such as Egypt.

Recently, Directive 2007/47/EC amended the AIMDD and MDD Directives, aligning the legislative elements governing both directives. The CE mark certifies that a product has met a specific set of regulations to ensure its safety and function. CE marking is not used exclusively for medical devices but is also required by other specific European directives for the marketing of many different products. In 2009, responsibility for medical devices within the European Commission transferred from the Directorate General for Enterprise and Industry (DG enterprise) to the Directorate General for Health and Consumer Affairs (DG Sanco), the governmental department responsible for health and consumers. In the EU, medical devices are organized into four classes according to their risk (I, IIa, IIb, and III), where I corresponds to the lowest risk and III to the highest. The level of risk is dependant upon the duration of use, the degree of invasiveness, whether the device is implantable, and whether it contains a substance active in its own right (e.g. drugs released by drug-eluting stents). Medical devices of all risk classes have to fulfil essential requirements (regarding safety and functionality related to the intended purpose).

Class I devices are self-certifiable devices like wheelchairs, materials like surgical gauze, adhesive bandages, etc. Class IIa devices include hearing aids and diagnostic ultrasound equipment. Class IIb devices include infusion pumps and surgical lasers. The devices with the greatest potential risk to patients are in class III; these include implantable prosthetic joints, drug-eluting stents and artificial heart valves.

All classes of devices above class I are required to involve a Notified Body relevant to the product to assess the compliance with regulations for safety and efficacy of a device. The Notified Body is responsible for conducting a third-party assessment of quality management systems and design methods for all class II devices and for each individual medical device in class III. Currently, there are over 80 Notified Bodies within the EEA. All were approved by the Competent Authority of the Member State where they are based *(1)*. Each nation in the EEA has its own Competent Authority that monitors product compliance with regulatory requirements for medical devices within its country. Manufacturers must seek their own Notified Body for their devices, and the Notified Bodies must be authorized and qualified to evaluate the device category. The devices are evaluated to ensure both safety and that they function as claimed by the manufacturer *(2)*.

The Notified Body is effectively responsible for pre-market evaluation of medical devices. They monitor all aspects of the evaluation from manufacturing process to post-market surveillance. They review all data (including clinical data), conduct regular inspections (including impromptu, on-site inspections) and collect reports regarding safety. Adverse event reporting to the Competent Authority is mandatory for the manufacturer. Once a device is reviewed and deemed acceptable, it receives the CE marking.

Currently, all EEA Member States require CE marking before the product is marketed and sold within their country. Along with public health safety, the economic benefit of a more-transparent trading system among European nations was the primary motive for implementing the CE marking system *(2)*. In fact, there are several countries that are not part of the EEA, but have entered into Mutual Recognition Agreements with the EU, which certifies their regulatory bodies as Competent Authorities to monitor safety and efficacy *(3)*.

Directive MDD 2007/47/EC requires clinical evaluation for all medical devices before they go to market. Such evaluation comes from clinical data, which can be obtained from clinical trials, scientific publications or through a documented clinical evaluation of an equivalent medical device. New technologies (devices) have to undergo clinical trials to prove their safety and efficacy. What constitutes a new technology is subject to debate. Those conducting the trials must weigh the risks and benefits of the new device on the one hand, with the decision to provide market access based on sufficient clinical proof of safety and performance on the other.

For devices in classes I through IIb (low to medium risk), companies can submit data on the safety and performance of the device together with recent scientific literature on its intended purpose. For devices in class III (including implantable devices) clinical studies are required, except where current clinical data already exist. Manufacturers have to submit the results from any clinical trial, but there is no obligation to discuss the design of the study with the Notified Body or a regulatory agency prior to the trial.

The Active Implantable Medical Devices Directive regulates active implantable devices, such as pacemakers and deep brain stimulation devices, which are considered high-risk medical devices; these will always be assessed by a Notified Body. Requirements are comparable to those for class III devices.

The In Vitro Diagnostic Directive contains a list of high-risk in vitro devices (such as HIV tests) that always need approval by a Notified Body.

The manufacturer has to demonstrate and document compliance with the regulations for all classes of devices. The manufacturer has to issue a declaration of CE conformity stating that all requirements of the conformity assessment have been satisfied. Foreign manufacturers have to appoint an authorized representative within the EEA in order to be in compliance with the regulations. Products developed both within and outside the EEA are registered into the databank of devices under the name of the manufacturer and the authorized representative. Domestic companies that are within the EEA register their device under the company name. This databank, the European Database on Medical Devices (EUDAMED), is maintained in Brussels *(4)*.

The United States

Unlike pharmaceuticals, which have been regulated by the Federal government since the beginning of the 20th century, the pre-market regulation of medical devices by the U.S. Food and Drug Administration (FDA) is a relatively recent phenomenon. In 1976, Congress enacted Medical Device Amendments to the Federal Food, Drug and Cosmetic Act partly as a response to growing concerns over the safety and effectiveness of medical devices. The Amendments classified new devices as low (I), moderate (II), or high risk (III) *(5)*. The regulatory process is similar to that described for the EU. As in the EU, medical technology regulated as devices in the United States includes items as simple as bedpans and latex gloves and as diverse and complex as magnetic resonance imaging (MRI) scanners, robots for surgery and drug-eluting stents. The Amendments gave the FDA oversight authority for the first time to regulate the clearance and approval of medical devices prior to marketing, as well as to enforce regulations on good manufacturing practices and post-market reporting requirements *(6)*.

Still, a difference exists between the introduction of new drugs and medical devices. While new drugs must pass rigorous pre-marketing clinical evaluation (generally with at least two randomized clinical trials), such an approach is usually not required for new devices. FDA approval for high-risk (class III) devices, however, requires at least one well-designed and controlled clinical study to establish the safety and effectiveness of the device. This different approach to pre-market clinical review of drugs and devices extends throughout the health-care system in the United States; for example, formulary committees for drug coverage have few device-coverage correlates. Recently, there has been a call in the United States to address the distinction between drugs and devices, in part through a federal centre for comparative effectiveness reviews *(7)*.

Within the FDA, the Center for Devices and Radiological Health (CDRH) has primary responsibility for the pre-market assessment of new medical devices. By any measure, this is not a trivial undertaking. The FDA has approved more than half a million medical device models produced by approximately 23 000 different manufacturers for a global industry of more than US$ 130 billion (€88 billion) per year. It has been estimated that in 1986, 4% of the population in the United States had at least one implanted medical device, and this percentage has surely increased significantly over the past two decades *(5, 8)*. The explosive growth in the use of medical devices in the United States is illustrated by the dramatic change in management of coronary artery disease: by 2002, surgeons performed more than twice as many percutaneous coronary intervention procedures (800 000) as coronary artery bypass graft surgeries (350 000) *(1)*.

The first step in the acquisition of clinical data for high-risk (class III) medical devices is for industry to obtain approval from the FDA for initial clinical testing. Significant risk devices include implants and life-supporting or -sustaining devices that have the potential for serious risk to the health, safety or welfare of a subject, or devices that are of substantial importance for diagnosing, curing, treating or mitigating disease (e.g. devices intended to diagnose or treat cancer). The more extensive regulatory requirements for significant risk devices often delay clinical testing by three to six months; when added to the additional several months it takes to get Institutional Review Board approval at the clinical site, some device manufacturers opt to test their devices outside of the US. For example, more than half of new cardiovascular devices developed by companies in the United States are first tested elsewhere *(1)*.

In the United States, low risk (class I) devices such as surgical gloves and hand-held instruments are subject to certain general regulatory controls, such as requirements for labelling, good manufacturing practices and registration of manufacturing facilities, and listing of devices with the FDA. Most are not required to undergo pre-market clearance through the 510(k) process (see below). The moderate risk posed by class

II devices (e.g. computed tomography [CT] scanners or endoscopes) requires that the sponsor comply with "special controls" in addition to the general controls required for class I devices *(5)*. For example, special controls may include adherence to performance standards, guidance documents or implementation of post-market surveillance measures, such as patient registries. Class III devices, such as pacemakers, cochlear implants and heart valves, pose the highest risks to patients and typically include implants that are life-sustaining/life-supporting and have the potential to inflict significant harm should they malfunction. They are subject to the most stringent levels of evaluation through the Premarket Approval Application (PMA).

Among the thousands of device applications submitted annually to the FDA/CDRH, fewer than 50 undergo a PMA, which is roughly analogous to the rigorous scrutiny required for new drugs *(9)*. Pre-market applications may be initiated via a Premarket Notification 510(k), an FDA process based on the argument that the device is essentially equivalent to one that has already been approved by the FDA; this pathway to market does not usually require clinical data derived from randomized trials regarding the effectiveness of a device for a given use or population of patients *(5, 10–12)*. For the new device to be considered "substantially equivalent" to the predicate device, it has to be demonstrated to be similar in design and intended use. If any technological characteristics differ from the predicate, the sponsor has to provide performance data to demonstrate that the changes do not raise new questions of safety and effectiveness, and that the new device is at least as safe and effective as the predicate device *(13)*. Performance data may range from bench data to those from controlled clinical studies, depending on the issues raised by the new technological characteristics of the device. Only approximately 10% to 15% of Premarket Notification 510(k) applications contain clinical data derived from human studies *(6)*.

For the fiscal year 2005, the Office of Device Evaluation reported receiving 3130 different 510(k)s (approximately 250 per month), whereas only 43 original PMAs requiring rigorous study were submitted *(9, 10)*. Many Premarket Notification 510(k) applications reviewed are for modifications to, or new features for commercially available devices. However, the Government Accountability Office reported that the FDA may be clearing too many high-risk devices through the less stringent 510(k) process. In September 2009, the FDA commissioned the Institute of Medicine to examine the strengths and weaknesses of its pre-market notification programme and issue recommendations for improving the system *(14, 15)*.

The PMA requires the manufacturer to submit clinical data to the FDA/CDRH that their device is safe (i.e. the probable benefits outweigh the potential risks) and effective for its intended use in the target population. The PMA application contains non-clinical information pertaining to the design and characteristics of the device, and a section on clinical investigations that includes safety and effectiveness data. The type of data required for approval ranges from multi-centre randomized clinical trials for the highest-risk devices to single site non-randomized cohort studies for devices deemed to be of lower risk (e.g. hip resurfacing implants or simple diagnostic devices such as ambulatory sleep apnoea monitors). The FDA may call on an advisory panel consisting of expert clinicians and scientists to review the clinical evidence for a new device and give recommendations, but the agency is not bound by those recommendations. The panel also includes an industry representative and a consumer representative (both non-voting panel members).

The Humanitarian Device Exemption (HDE) regulatory pathway is also available for devices that are intended to benefit patients by treating or diagnosing a disease or condition that affects fewer than 4000 individuals in the United States per year (called a Humanitarian Use Device, HUD). An HDE application is similar in both form and content to a PMA, but is exempt from the effectiveness requirements of a PMA. An HDE application, however, must contain sufficient information for the FDA to determine that the device does not pose a significant risk of illness or injury, and that the probable benefit to health outweighs the risk of injury or illness from the device's use, in the context of probable risks and benefits of currently available devices or alternative forms of treatment. Additionally, the applicant must demonstrate that no comparable devices are available to treat or diagnose the disease or condition, and that the manufacturer could not otherwise bring the device to market. The labelling for an HUD must state that the device is a humanitarian use device, and that although authorized by Federal Law, effectiveness of the device for the specific indication has not been demonstrated.

Post-market surveillance of medical devices

The goal of post-market surveillance is to monitor safety and effectiveness after a device has been marketed. This is a large, critically important, and underfunded task. Because pre-market clinical studies generally have limited numbers of participants followed for a short period of time, they may be unable to detect rare but serious adverse events or long-term failures. Devices are often used in patient populations that differ from those studied in pre-market studies, so implementing post-market surveillance to evaluate the benefits and risks in populations beyond those included in the initial evaluation is important contribute to a continuous evaluation. Since clinicians skilled in the use of the device conduct such trials, the learning curve associated with the device is not necessarily considered in daily practice; surveillance, then, may be able to detect complications related to inexperience with, and improper use of a device. It would also be valuable for post-market surveillance to include 'off-label use' of medical devices, as there is no other source for outcomes data available for these populations. Finally, post-market studies can identify problems arising from the manufacturing process, including those related to quality control in a production run of an existing device or those arising from modification of a device.

The European Union

In the EU, post-market surveillance and adverse event reporting are two complementary obligations of the manufacturer to monitor the safety and effectiveness of medical devices. Post-market surveillance consists of active monitoring of medical devices during their use. Serious adverse events – those that led (or might have led) to one of the following outcomes: death of a patient, user or other person, or serious deterioration in state of health of a patient, user or other person – must be reported to the Competent Authorities.

All stakeholders, from manufacturers to distributors and providers (and in some countries any person aware of the event), are required to report adverse events to the Competent Authority. The Competent Authority must further report adverse events to the EC and the Notified Body that has issued a CE certificate for the product. This ensures that adverse event reporting will occur in all nations in which the product is being marketed and sold, and not just the country in which the Notified Body of the product resides.

For all products above class I, a plan to collect post-market clinical data must be in place before CE marking is approved. Data collected post-market must then be sent to the Notified Body for analysis. Notified Bodies are also called upon to make unannounced visits to the manufacturer's site as part of quality surveillance. These regulations ensure the safety of a product and that the product functions as the manufacturer claims. However, regulations say nothing about effectiveness or cost-effectiveness. Decisions about whether the value of a particular medical device merits coverage are up to the discretion of each nation and the reimbursing agencies within them.

Reimbursing agencies generally require further assessment of the effectiveness and cost-effectiveness of a particular device beyond that required for CE marking *(32)*. Thus, almost all devices are subject to further scrutiny.

The United States

The Medical Device Reporting (MDR) programme requires device manufacturers to have a system in place for reporting adverse events associated with medical devices and to report to the FDA any significant safety concerns. User facilities and importers are required to report device-related deaths directly to the FDA and the manufacturer; importers are also required to report serious injuries to both. In addition, user facilities report serious injuries and importers report malfunctions to the manufacturer. The FDA maintains a central database called the Manufacturer and User Facility Device Experience Database (MAUDE) to collect data on adverse events from users (clinicians and facilities) as well as from industry and the general public.

Most experts agree, however, that the current system is plagued by significant underreporting of adverse clinical events *(5, 33)*. In 2002, for example, while the FDA received more than 120 000 adverse event reports, only 5% originated from clinical facilities, health professionals or consumers. Of the reports submitted by health professionals, the majority are from nurses *(5, 10)*. In addition to underreporting, MAUDE is limited by incomplete, non-validated data, the lack of incidence data, uncertainties about causality, and biased reporting.

Despite these limitations, the system can work effectively. For example, in April 2003, the FDA approved the first drug-eluting stent based on pre-market testing in 673 patients. Over the next five months, nearly 300 cases of in-stent thrombosis were reported, including 60 deaths *(34)*. This resulted in an FDA alert to clinicians released on 29 October 2003 *(35)* and a flurry of clinical investigations and reports evaluating the incidence of in-stent thrombosis *(36–41)*. The system worked, in part, because more than 250 000 stents were used during that five-month period. Clearly, adverse event reporting and evaluation is crucial to the safe use of medical devices.

In 2002, the CDRH established the Medical Product Safety Network (MedSun)[1], a network of 350 clinical sites (mostly

1 http://www.medsun.net/ (accessed 22 February 2010).

hospitals) trained to be more proactive and thorough in capturing adverse events of devices. The goal of MedSun is to directly interface with the user community, address some of the limitations of the passive MDR system, and to capture important 'near-miss' events that may alert the FDA and manufacturers to potential problems before catastrophic events occur.

The reliance on a passive reporting system for post-market surveillance of medical devices has spurred much debate and calls for reform *(10, 42, 43)*, recently prompting the FDA to re-evaluate and expand its approach to post-market surveillance *(6)*.

It is important to remember that the FDA mandate explicitly does not include the regulation of physician behaviour *(44)*. Once a technology is approved, it can be used in clinical scenarios that fall outside the evidence-based criteria of the pivotal clinical trials. For example, in the recent controversy over the long-term safety of drug-eluting stents, it was revealed that these devices frequently are implanted for off-label indications *(45)*.

Methodology for prioritizing and evaluating medical devices

Fundamental differences between medical devices and pharmaceuticals have led to different approaches for prioritizing and evaluating devices and drugs. Drugs, generally taken on a daily basis, are usually cleared from the body within hours to days. Implanted medical devices may remain in the body for years or decades, and may not be easily removed. Drugs, once approved, often remain on the market for years without any fundamental change, while devices tend to have small refinements made every year or two.

Additionally, the benefits and risks associated with the use of a new device may depend heavily on the skill of the user (health-care professional or patient). Evaluating the net risks and benefits of a device may need to factor in the learning curve associated with it. The risks associated with many devices may lead to recommendations that the new device be used only in 'centres of excellence' – clinics in the United States with sufficient volume and expertise to achieve the promised benefits of the device. In the United States, differences in the level of clinical evidence required for pre-market FDA approval between drugs and medical devices has sometimes led to a higher level of scrutiny by health insurance providers in deciding whether or not to cover new medical devices.

Prioritizing devices for assessment

Technology assessment is a time- and resource-intensive process, so it is important for decision-makers to be judicious in choosing devices for thorough evaluation. There is no set algorithm to guide which devices to assess and to what degree. In general, devices with the potential for large clinical benefits or those that have significant cost implications are prioritized. Given the value judgments and potential biases inherent in this process, it is essential that multiple viewpoints be represented in the assessment and decision, including those of patients and their advocates, specialists, policy-makers and clinicians.

Health technology assessment

Several organizations have codified in great detail their approach to health technology assessment (HTA): their similar basic steps have become standard. In general, there are three phases: scoping, assessment and appraisal *(16)*.

Phase one: scoping

The first step is to clearly define the questions and target groups to be addressed in the assessment. The patients, interventions, comparators, outcomes, timing and setting to be evaluated have to be clearly specified. The indications for the device, views of experts (as well as those of patients) and claims about the advantages of the new device could all be considered when weighing its benefits and risks.

The scope of an assessment may go beyond the target population, comparators, and outcome measures included in pre-market studies. For example, drug-eluting stents were initially evaluated for use in symptomatic patients with proximal, single vessel, coronary artery disease in a native blood vessel with a diameter of 2.5–3.5 mm. But these stents can also be used in patients with more complex stenoses: those with smaller blood vessels or stenoses in bypass grafts. Of course, it is important for the currently accepted standard treatment(s) for the indication to be considered. For example, bypass surgery, bare metal stents, angioplasty without stenting, and medical management are all potential alternative therapeutic interventions that can be considered when evaluating the use of drug-eluting stents.

During the assessment, it is valuable for the emphasis to be on outcomes that are clinically meaningful to patients (e.g. heart attack, stroke, fracture, cancer recurrence, death, fewer hospitalizations, fewer days on ventilator, quality of life, and/or level of disability) and not on surrogate markers for these outcomes (blood pressure, lipid levels, bone mineral density, plaque regression and/or tumour regression). Surrogate markers are often used for pre-market approval of devices, but even markers that are generally thought to be valid have been wrong in some cases (e.g. fluoride increases bone mineral density, but raises rather than lowers the risk for clinical fracture; the drug torcetrapib raises high-density lipoprotein levels, but increases the risk of adverse cardiovascular events and death). The most important benefits and risks can be specified and those outcomes critical to the overall assessment of the device can be highlighted. It is preferable that all stakeholders – including manufacturers, specialists who may use the device, patient groups and organizations providing health-care coverage – have input into specifying these outcomes.

Phase two: assessment / systematic literature review

The next step is to evaluate the evidence available on a technology. Traditional reviews and "dossiers" prepared by manufacturers *(17–19)* may select only studies that support a particular point of view or emphasize particular outcomes while ignoring others. By contrast, a comprehensive, systematic assessment of all clinical studies of the device avoids bias in the identification, selection and interpretation of research evidence. The goal is to provide a thorough, unbiased synthesis of the available evidence that defines the new device's strengths and limitations, and if possible, provide best estimates and ranges of uncertainty for its clinical efficacy and cost-effectiveness. Systematic evaluations of the literature vary in scope, ranging from narrowly focused systematic reviews of randomized trials to comprehensive evidence reports, comparative effectiveness reviews and technology assessments that assess a

broader range of studies, and examine each assumption in the logic linking use of a device to health outcomes *(20)*.

Methods for conducting systematic reviews also vary. For example, to identify studies, some organizations search for unpublished data available in abstracts from meetings, the FDA web site and manufacturers. This is done in order to limit publication bias and to be as comprehensive as possible. Other groups explicitly exclude unpublished data because it is not peer reviewed, often incomplete, and may present a biased assessment of the data. Requiring published data also creates an incentive for health technology assessment agencies to publish their study results quickly. Similarly, methods to assess the quality of individual studies vary. A review by the Agency for Healthcare Research and Quality (AHRQ) identified 121 different systems to evaluate the quality of individual studies and rate the overall strength of the scientific evidence *(21)*.

Organizations also differ in how they define eligible evidence. Ideally, decisions about the clinical efficacy of new devices would come from peer reviewed publications fully reporting on several large, multi-centre randomized trials that compare the new device to the current standard of care over a time period long enough to assess the expected natural history of the disease. However, these data are rarely available. More commonly, there are only data from case series compared to historical controls. There may be data only on intermediate outcomes, such as blood vessel diameter post-stenting or the rate of restenosis evaluated by endoscopic ultrasound, rather than clinical outcomes such as recurrent heart attacks or angina two years after stent placement.

Observational data should not be undervalued. Large case series with long follow-up are often the best source of data for the true incidence of adverse events associated with a device, particularly for patient groups excluded from the initial clinical trials. Consistent data from multiple high-quality observational studies that demonstrate a very large treatment effect can provide strong evidence for the efficacy of a medical device *(22)*. An example is the 69% reduction in serious head injuries with the use of bicycle helmets reported in a meta-analysis of observational studies *(23)*.

Because conducting systematic reviews is an evolving science, methods cannot be fully harmonized. Precisely for this reason, it is preferable for organizations to use explicit, detailed guidelines for conducting systematic reviews. The goal of this guidance is to limit bias at every stage of review, from developing the essential questions to summarizing or synthesizing results (and all steps in between). When possible, it is preferable for guidance to be based on empirical methodological research. When research does not provide a clear answer, guidance can contain structural approaches to avoiding bias *(24)*. In the United Kingdom of Great Britain and Northern Ireland, guidelines for technology appraisal from the National Institute for Health and Clinical Excellence (NICE) exemplify this approach *(16)*. In the United States, AHRQ recently issued draft guidelines for comparative effectiveness reviews *(25, 26)*.

Assessing cost-effectiveness

Randomized clinical trials rarely capture the economic data needed to evaluate the incremental cost-effectiveness of a new device compared with the accepted standard of care. Thus, some form of modelling is usually necessary to estimate the cost-effectiveness of a new device. Furthermore, data on local patient characteristics, standards of care, costs and resource constraints differ across different health-care systems. However, it is preferable for the general structure of such models to be similar across health systems, with appropriate changes made to the model to reflect system-specific data.

The most common economic model performed for health-care outcomes is a cost-utility analysis. This type of analysis converts all outcomes into a common metric, the quality-adjusted life year or QALY, and allows the model to estimate the incremental cost per QALY associated with use of the new device. The data required for such cost-utility analyses include estimates for the efficacy of the device compared with the standard of care in regards to all major benefits and risks associated with use of the device. In addition, the associated effects of those potential benefits and risks on a patient's quality of life must be quantified whenever possible. It is also important for the costs of the device to be quantified and compared to the device's impact on the costs of the disease being treated.

There may be uncertainty about the magnitude of many of the inputs to the model. This uncertainty can be evaluated in several ways. First, the impact of changes in each of the individual inputs can be evaluated in a series of one-way sensitivity analyses. This helps to identify critical factors driving the cost-effectiveness of the intervention. Next, the overall uncertainty can be estimated using probabilistic modelling techniques. In brief, probabilistic modelling reruns the model hundreds of times using different estimates for all model inputs based on the uncertainty around each estimate. The cost and QALY from each model are plotted on a graph to give a pictorial representation of the precision of the estimated cost-effectiveness of the intervention.

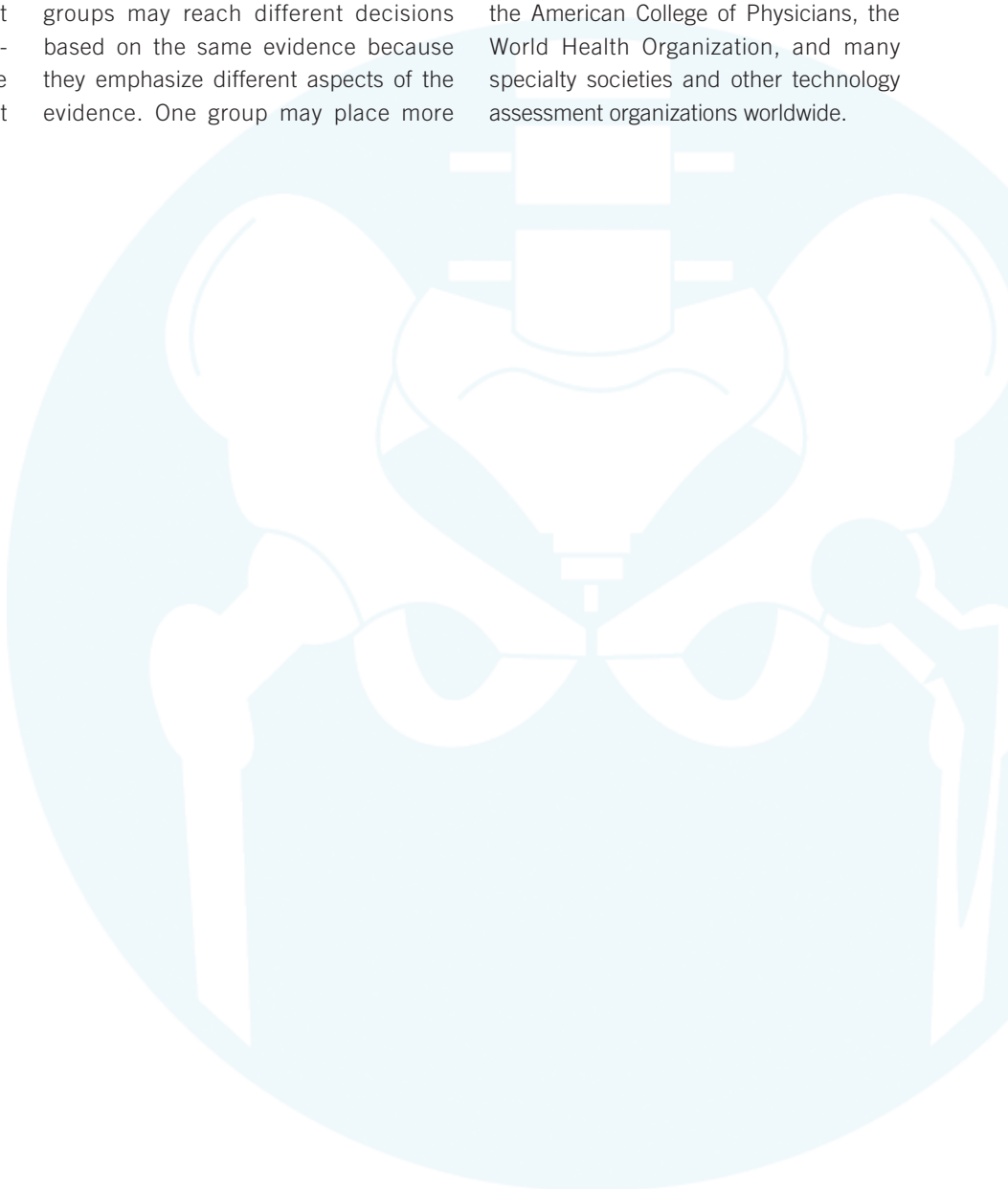
Phase three: appraising the device or service

The appraisal process has been defined as "a multidisciplinary field of policy analysis, studying the medical, economic, social and ethical implications of development, diffusion and use of health technology" *(27)*. Drummond et al. go on to state that the appraisal process "inherently requires consideration of the integration of medical interventions into clinical care and, as such, requires consideration of the specific contexts (e.g. care practices and structure; prices) in which the technology will be used, as well as societal factors (e.g. population health state preference values)" *(27)*. The final decision-making process often considers the seriousness of the disease state and the availability of alternative therapies. Thus, decision-makers may have different standards when appraising the evidence for a new device allowing delivery of effective therapy for pancreatic cancer, compared with the evidence for a new treatment for plantar fasciitis. It would be valuable for policy-makers to fully consider the results of the assessment of clinical efficacy and cost-effectiveness. These data can be appraised

in light of additional input from expert commentators, clinical specialists, patient advocates and manufacturers. This will allow policy-makers to make judgments grounded in evidence and make decisions that reflect the values of the population they represent.

If there is high-quality evidence demonstrating that a new device clearly saves lives and results in net cost-savings for the health-care system, there is little controversy over the decision to approve its use. More difficult decisions arise when preliminary data suggest that an expensive device improves short-term quality of life or other intermediate outcomes, but uncertainty remains about long-term outcomes. This was the case in 2002 for biventricular pacemakers used in patients with heart failure and conduction abnormalities *(28)*. Some health systems began using the devices in 2002 and 2003, while others waited until 2004 when there was unequivocal data from multiple clinical trials demonstrating a mortality benefit in carefully selected patients *(29, 30)*.

In most cases, uncertainties about the magnitude of the clinical benefits, long-term outcomes, and cost constraints make the final appraisal very difficult. Different groups may reach different decisions based on the same evidence because they emphasize different aspects of the evidence. One group may place more weight on making a potentially valuable device available as soon as possible, while another group may feel that uncertainty about adverse events associated with its prolonged use must be resolved prior to coverage. As recommended by the Grading of Recommendations Assessment, Development and Evaluation (GRADE) working group, the transparency of the appraisal process is enhanced if such value judgments are made explicit in the language of the final appraisal *(31)*. Organizations that have endorsed the GRADE approach include the Cochrane Collaboration, NICE, the American College of Physicians, the World Health Organization, and many specialty societies and other technology assessment organizations worldwide.



Information resources for clinicians and health-care organizations

Medical technology assessments may amplify conflicts of interest related to investments, reimbursement for clinical services, research support, political and lobbying influences, and other factors affecting all stakeholders: manufacturers, stockholders, physicians, patients, insurance carriers and even the FDA itself. Existing medical technology assessment groups provide complementary critical analyses of the efficacy and safety of new medical devices. Among the government-sponsored organizations in the United States that produce technology assessments and other systematic evidence reviews, the most prominent is AHRQ. The 14 AHRQ-supported Evidence-based Practice Centers serve as the primary source of assessments for the U.S. Preventive Services Task Force and the Effective Health Care Program. Evidence-based Practice Centers also conduct assessments for the Centers for Medicare and Medicaid Services (CMS), which often initiates coverage of medical devices with an evidence-development process ultimately aimed at synthesizing large amounts of data from various clinical experiences *(46)*. Other groups that produce technology assessments include the Institute of Medicine (IOM), the National Institutes of Health (NIH) and the U.S. Department of Veterans Affairs. Outside the United States, there are a large number of regional and national health technology assessment agencies that often determine whether or not a medical device should be covered based on local needs and resources. Some well-known examples include NICE in the United Kingdom, the Canadian Agency for Drugs and Technologies in Health (CADHT) and the Danish Centre for Health Technology Assessment (DACEHTA). Finally, there are a number of for-profit technology assessment and forecasting groups that may help organizations make informed decisions about new technologies, including medical devices.

Insurance companies in the United States rely on a mix of both proprietary and publicly available technology assessments for their policy development; some have their own proprietary technology assessment process or purchase proprietary technology assessments produced by independent, often for-profit, companies.

Professional societies oversee the utilization of new technologies that fall under their domain, and they frequently provide checks and balances on other decision-making entities. Their web sites can serve as a forum for differing views on complex topics that affect patient safety *(47, 48)*. Professional societies have often taken the lead in endorsing evidence-based reviews *(49)*. In addition, some professional societies have been strong advocates for applying and refining standard criteria for conducting systematic reviews with the aim of developing practice guidelines *(50, 51)*. Professional societies not only provide a format for discussion, they also work towards improving the overall quality of debate. However, as with other evaluative entities, they are not immune to pressures and financial conflicts of interest that may influence their recommendations *(52, 53)*.

Global harmonization

There is growing interest in creating a uniform set of standards for medical device regulation. The Global Harmonization Task Force (GHTF) aims to achieve just this. It began in 1992 as a partnership of five regions: Australia, Canada, the EU, Japan and the United States; these regions constitute more than 90% of the world market for medical devices *(61)*. The goals of the organization are to enhance medical device safety through the promotion of uniform standards for pre- and post-market regulation, and to foster innovation and global trade by reducing redundant or conflicting regulatory standards. The GHTF periodically produces recommendations within their task groups for member countries to promote regulatory harmonization, but these are not binding *(54)*.

Gaps and barriers to high-quality clinical evidence for medical devices

One of the major challenges in understanding the balance of risks and benefits for medical devices is the lack of high-quality information on rare but serious complications. Initial clinical trials prior to marketing are generally too small to identify uncommon complications. Post-market surveillance depends on passive reporting of adverse events, which suffers from underreporting and lacks data on the number of devices at-risk for the adverse event. Thus, it is impossible to calculate the incidence of the adverse event and place it in the context of a device's known benefits and risks.

A commonly cited concern, particularly for drugs, is that the manufacturers do not publish or make publicly available data on critical outcomes they have collected from clinical trials. This problem has prompted many to call for mandatory registration of all clinical trials for drugs *(55–58)*, although the extension of this requirement to medical devices has been debated *(59)*.

When randomized clinical trial evidence is available, it usually represents the results obtained in a sample of patients who have been recruited to maximize the chance of demonstrating efficacy with the new device. The investigators often exclude patients with significant co-morbidities, older patients, children and patients likely to experience side-effects. Data from a more representative sample of society are usually limited.

Conclusions

The primary goal of the pre-market approval process is to protect the safety of patients who will potentially benefit from a new device. The randomized controlled trial has historically been the 'gold standard' for therapeutic interventions in medicine. The risks and benefits of many drugs are evaluated using this method. Such trials can be performed with many new medical devices, but can also prove to be quite challenging in many cases. It is often impossible or unethical to use placebos or conduct unnecessary ('sham') operations, and sometimes pre-existing interventions are unavailable for use in comparison with new devices. Even settling on the proper number of experimental patients and the process of randomization may be difficult for certain types of clinical studies evaluating new devices. In these cases, it may be valuable for regulatory agencies to develop models for clinical trials specific to medical devices. Such standard models would allow for the comparison of old and new devices when possible, and recognize the potential for 'first-in-man' trials addressing clinical indications that do not yet have established surgical or pharmaceutical standards of care.

In regards to high-risk devices, it would be valuable for regulatory agencies to ensure, whenever possible, that high-quality randomized trials are completed prior to granting marketing approval. Such trials can be feasible: for example, many payers in Europe and the United States did not approve coverage of drug-eluting stents or biventricular pacemakers until there were several years of follow-up data from large randomized trials. Similarly, the FDA in the United States has required manufacturers of artificial spinal discs to conduct randomized trials comparing the new devices to spinal fusion surgery.

Improving the systems of post-market evidence-generation and surveillance can be valuable to ensure high-quality clinical evidence for assessing the relative value of new devices. In situations where the use of devices is to be extended beyond patients eligible for the original clinical trials, where high-quality randomized trials were performed prior to widespread adoption of the new devices (e.g. biventricular pacemakers, implantable cardiac defibrillators, drug-eluting stents), high-quality observational studies can be used to evaluate the effectiveness of the devices in new populations.

Incentives play a central role in catalysing the generation of evidence. In order to increase the incentive for manufacturers to complete high-quality post-market studies, continued marketing approval of a new device could be contingent upon the successful completion of a study meeting a regulatory body's criteria for size, length of follow-up and data quality. In order for this to work effectively, regulatory authorities could revoke marketing approval for any device whose manufacturer fails to comply with the required study. Another potential incentive for manufacturers is the expanded use of devices, which could be permitted by regulatory authorities only with proper evidence development. In addition, the presence of health plans that offer coverage for devices, within clinical trials that aim to establish risks and benefits associated with the device, could promote evidence development. Thoughtful application of this combination of potential incentives and penalties could improve the quantity and quality of clinical evidence for new devices.

A second approach could be to create systems within large health-care organizations or countries with national data systems to track use of new devices. The clinical indications for which the device is used could be monitored to assess the degree of off-label use. More importantly, long-term outcomes could be monitored to assess both the clinical efficacy of the device as well as unexpected complications and device-failure rates in a 'real-world' setting. Administrative datasets, such as Medicare claims data in the United States, have the potential to help generate more representative clinical data *(60)*.

A recent publication detailed many of the principles that could form the foundation of high-quality technology assessment *(27)*. The authors, who are all members of the International Group for HTA Advancement,[1] enumerated 15 principles to guide the organization, methodology and processes of HTA, and the use of HTAs in decision-making. The key principles are to ensure a timely, unbiased and transparent process, and to involve all key stakeholders in every step of the process, from defining the scope of the assessment to the economic analysis and value judgments underlying the final decision-making.

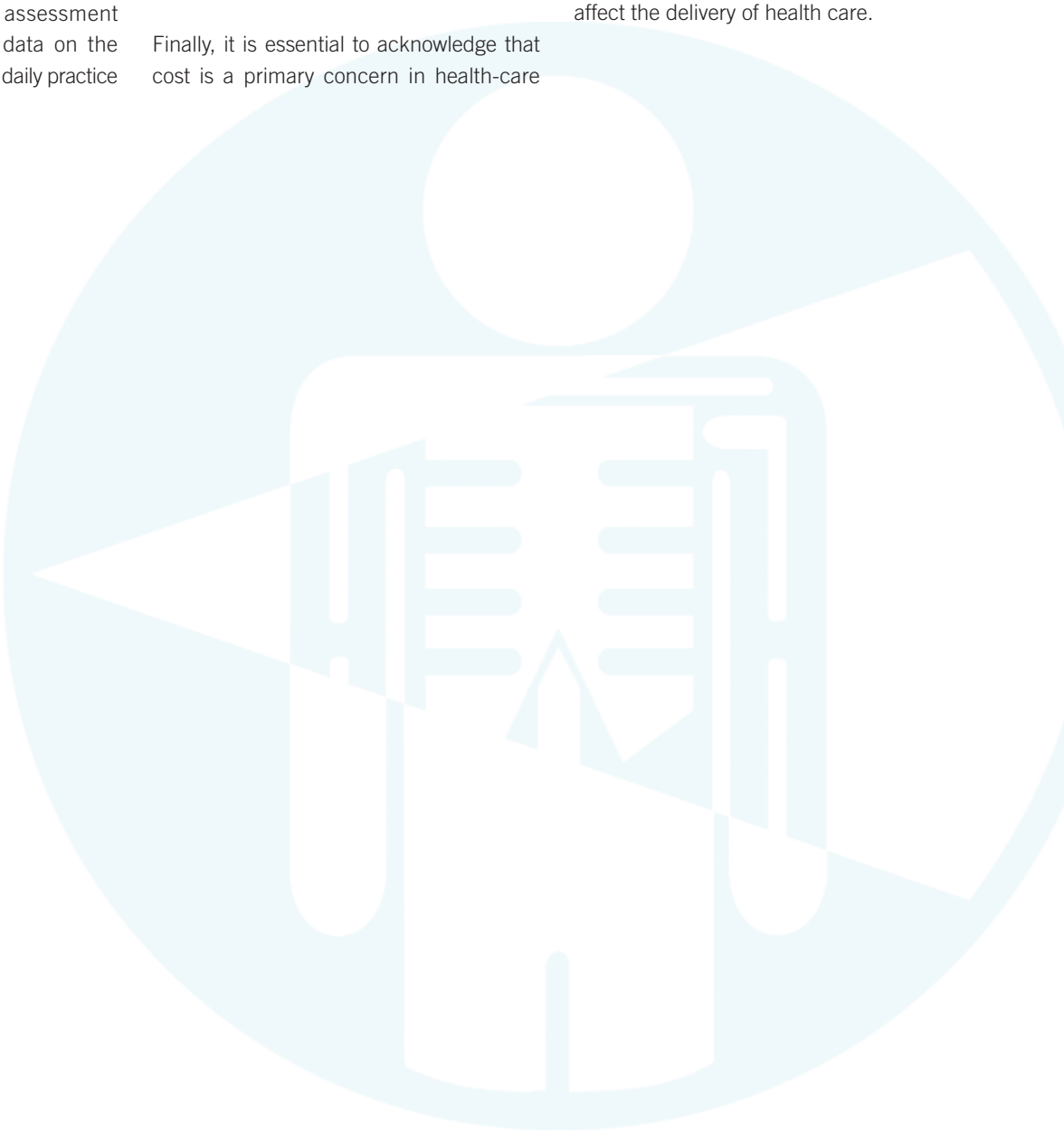
The methods for assessing and appraising evidence continue to evolve. It is important that the methods used be explicit and transparent. It would be valuable for judgments made at each step in the process to be explicitly documented so that disagreements in interpretation can be openly debated. The technology assessment process gathers and synthesizes evidence in similar ways across all health systems – part of a continuing trend towards a standard approach to data collection. The GRADE approach is an example that is being accepted by a growing number of organizations. The Working Group's summary tables and quality assessment approach could be the basis for a unified approach. This would significantly decrease the duplication of efforts involved in performing systematic reviews and extracting data from clinical trials. The appraisal process, on the other

1 http://www.inahta.org/HTA (accessed 22 February 2010).

hand, is dependant on local values, disease epidemiology, costs and resources. Thus, final appraisals of medical devices cannot be generalized across health systems.

The evidence base for new devices continues to expand after the initial assessment and appraisal. Indeed, the data on the effectiveness of new devices in daily practice can only be evaluated after the device has been widely available. It is incumbent upon organizations performing HTAs to reassess the evidence base periodically and to update the assessment when significant new data become available.

Finally, it is essential to acknowledge that cost is a primary concern in health-care systems worldwide and a key driver of technology assessment. Therefore, cost-utility analyses are an integral part of any health technology assessment. Ultimately, the quality of these and other assessment data will guide decisions that significantly affect the delivery of health care.



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