Examining the National Regulatory Environment of Medical Devices: Major Issues in the Risk–Benefit Assessment of High-Risk Devices

*Ghislaine Mathieu & Bryn Williams-Jones**

High-risk medical devices (MDs) are mostly used as last-resort treatment or in surgical procedures. Their approval by national regulatory bodies depends essentially on their quality, safety, and efficacy for a particular clinical indication. In our study, we examine the national regulatory processes of the five founding members of the former Global Harmonization Task Force (replaced by the International Medical Device Regulators Forum in 2012) – Australia, Canada, the European Union, Japan, and the United States – with a view to identifying which uncertainties associated with high-risk devices raise sufficiently serious ethical concerns to warrant more robust regulatory oversight and governance. The assessment of the safety and effectiveness of high-risk medical

L'utilisation d'un dispositif médical (DM) à risque élevé nécessite souvent une procédure chirurgicale pour traiter un problème de santé majeur. La décision d'autoriser la mise en marché de ce type de DM relève des organismes nationaux de réglementation et s'appuie sur l'examen des données qui démontrent leur innocuité et leur efficacité pour un usage défini. Les nombreux rappels observés au cours des dernières années semblent témoigner des faiblesses dans cet examen, particulièrement pour les DM à risque élevé, avant et après leur mise en marché, en raison des difficultés pour obtenir des données robustes et fiables quant à leur innocuité et leurs bénéfices réels. Nous avons examiné les processus réglementaires des cinq ju-

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devices is a challenging issue, during both the premarket and post-market phases of evaluation, because there may be a lack of robust and reliable evidence to demonstrate long-term safety and effectiveness, as seen in the many product recalls in recent years (e.g., hip replacement prostheses). Faulty devices can have a significant negative impact on patients and the broader public. The deployment of unsafe or ineffective medical devices raises questions about the extent to which manufacturers, regulators, and clinicians attend to fundamental ethical principles of medicine, such as informed consent, beneficence, and non-maleficence. Respect for these principles is essential to facilitating optimal decision making by patients and clinicians who are considering recourse to a procedure involving the use of a high-risk device; failure to respect these principles can undermine public confidence in clinicians, manufacturers, and regulators. We therefore suggest some avenues to improve the current regulatory requirements and practices for high-risk devices, specifically with regard to how evidence is assessed at both the premarket and postmarket levels.

risdictions membres du *Global Harmonization Task Force*, mis sur pied au cours des années 1990 en vue d'harmoniser les pratiques nationales en matière de réglementation des dispositifs médicaux : l'Australie, le Canada, l'Union européenne, le Japon, les États-Unis. Nous voulions identifier les faiblesses des processus de réglementation actuels et positionner les enjeux éthiques autour des pratiques associées à ces processus, afin d'expliquer la nécessité de renforcer ces pratiques. Des DM défectueux ou inadéquats, non sécuritaires ou encore inefficaces peuvent avoir un impact important pour la santé des patients et affaiblir la confiance du public en général à l'égard des manufacturiers, des organismes réglementaires et des professionnels de la santé. En outre, les pratiques actuelles concernant l'examen des données cliniques interpellent les principes éthiques fondamentaux associés à la pratique médicale et une prise de décision éclairée, à savoir le consentement éclairé, la bienfaisance et la non-malfaisance. Nous proposons des avenues pour renforcer les pratiques entourant les processus réglementaires actuels, en particulier pour ce qui concerne les DM à risque élevé, tant au cours de leur évaluation avant mise en marché que lors de leur suivi après mise en marché.

Introduction

In a context of globalized heath technology innovation and an increasing demand for and use of an ever expanding number of medical devices (MDs) – including a growing number of high-risk, innovative, and implantable MDs (e.g., deep brain stimulation (DBS) or cardiac pacemakers) – it is important to examine how current national regulatory requirements ensure the safety, effectiveness, and reliability of MD. Unlike pharmaceutical drugs, MDs do not typically achieve their intended purpose through chemical action or immunological or metabolic means.[1] MDs are mechanical in nature and have no metabolic effect on the human body. Further, unlike pharmaceutical drugs – which have an extensive product life cycle involving decades of research and development and marketing applications – MDs have a relatively short product life cycle.[2] Some devices are extremely sophisticated and very expensive, and may involve the use of complex procedures by experienced health care providers (e.g., DBS). The MD sector involves hundreds of thousands of products, ranging from simple thermometers to more sophisticated items such as surgical instruments, pacemakers, and imaging equipment. But even some commonplace objects can be considered MDs if they are labelled or otherwise promoted for health-related purposes. For example, the US Food and Drug Administration (FDA) could regulate an iPod as a MD if it were labelled for treating stress or hypertension.[3] Some topical creams may also be regulated as devices – instead of as pharmaceutical products – because they do not contain any active ingredient and involve no chemical or metabolic action in the body (e.g., hyaluronic acid (Restylane) that is injected into the skin to fill moderate to severe wrinkles).[4]

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1 World Health Organization, *Health Technology Assessment of Medical Devices*, WHO Medical Device Technical Series (Geneva: WHO Press, 2011) at 5, online: <apps.who.int/medicinedocs/documents/s21560en/s21560en.pdf>.

2 Industry Canada, "Life Science Industries: Medical Devices – Industry Profile" (27 February 2013), online: <www.ic.gc.ca/eic/site/lsg-pdsv.nsf/eng/h_hn01736.html>.

3 Deborah E Tolomeo & Laurie A Clarke, "Medical Devices: The Obvious, the Readily-Accepted, and the Surprising" (2008) 1:4 J Health Life Sci Law 117 at 142.

4 Burgunda V Sweet, Ann K Schwemm & Dawn M Parsons, "Review of the Processes for FDA Oversight of Drugs, Medical Devices, and Combination Products" (2011) 17:1 J Manag Care Pharm 40 at 46–47.

Interestingly, while concerns about ethical issues – e.g., ensuring informed consent in clinical trials, the beneficence/non-maleficence of certain experimental products, justice in access to health services – and the appropriate regulation of pharmaceutical drugs have received significant attention in the bioethics and health policy literatures, there has been relatively little work addressing the concerns that are particular to new MDs and their integration into health care systems.[5] For example, advances in the neurosciences, bioengineering, and nanotechnologies have led to major innovations that raise challenging social, ethical, and policy questions (e.g., brain-machine interfaces extending the use of brain stimulation to the treatment of chronic diseases or enhancement of normal brain function), and these have received much attention in the academic and policy communities.[6] Yet there has been surprisingly limited attention paid to these issues on the part of health technology assessment (HTA) agencies that are responsible for conducting reviews and producing recommendations that can inform decision makers about the appropriateness of integrating certain new MDs into health care systems.[7]

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5 Sue Ross et al, "Ethics, Economics and the Regulation and Adoption of New Medical Devices: Case Studies in Pelvic Floor Surgery", online: (2010) 11 BMC Med Ethics 14 at 3 <www.biomedcentral.com/content/pdf/1472-6939-11-14.pdf>.

6 See e.g. Karim Jebari, "Brain Machine Interface and Human Enhancement: An Ethical Review" (2013) 6:3 Neuroethics 617; Thomas Fuchs, "Ethical Issues in Neuroscience" (2006) 19:6 Curr Opin Psychiatry 600; Sheri Alpert, "Brain–Computer Interface Devices: Risks and Canadian Regulations" (2008) 15:2 Account Res 63; Martha J Farah et al, "Neurocognitive Enhancement: What Can We Do and What Should We Do?" (2004) 5:5 Nat Rev Neurosci 421; Rutger J Vlek et al, "Ethical Issues in Brain–Computer Interface Research, Development, and Dissemination" (2012) 36:2 J Neuro Phys Ther 94.

7 See Devidas Menon & Leigh-Ann Topfer, "Health Technology Assessment in Canada: A Decade in Review" (2000) 16:3 Int J Technol Assess Health Care 896 at 896–902; Sigrid Droste & Ansgar Gerhardus, "Ethical Aspects of Short Health Technology Assessments: A Systematic Review" (2003) 97:10 Zeitschrift für ärztliche Fortbildung und Qualitätssicherung 711; Pascale Lehoux et al, "Redefining Health Technology Assessment in Canada: Diversification of Products and Contextualization of Findings" (2004) 20:3 Int J Technol Assess Health Care 325 at 325–36; Deirdre DeJean & Mita Giacomini, "Ethics in Canadian Health Technology Assessment: A Descriptive Review" (Presentation delivered at the Canadian Agency for Drugs and Technologies in Health 18th Symposium, 23–24 April 2007).

Our paper addresses issues that are specific to *in vivo* high-risk MDs first because in recent years some of these have proven particularly problematic for regulators in terms of both the incidence and potential magnitude of harm for patients, but also because of their cost implications for health care systems and third-party payers (e.g., public or private insurers). While the cost implications of new MDs are clearly a major concern for patients, public policy makers, and third-party payers, we restrict our analysis in this paper to those issues that are within the remit of national regulators, i.e., the current practices for assessing the safety and effectiveness of high-risk MDs where there is a reasonable possibility that their use may cause serious adverse health consequences.[8]

In our study, we examine the regulatory processes governing MDs in the five founding members of the former Global Harmonization Task Force (GHTF) – Australia, Canada, the European Union (EU), Japan, and the United States (US) – the creation of which was initiated by Canada. The GHTF became the International Medical Device Regulators Forum in 2012.[9] The aim of our study was to develop an understanding of international regulatory processes, with particular attention paid to premarket assessment rules and post-market follow-up mechanisms for high-risk MDs and "active implantable" MDs, in order to identify potential differences between the practices of national regulators, including gaps in current processes (e.g., risk classification, premarket evaluation activities, and post-market enforcement practices). High-risk MDs are often very complex technologies and frequently used as last-resort procedures for patients seeking relief

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[8] We have excluded *in vitro* diagnostic MDs from our study. Some of those may be the object of another study as they also raise socio-ethical and legal issues associated with their specific intended use (e.g., genetic-screening MDs).

[9] The Global Harmonization Task Force held its first meeting in January 1993 and was a voluntary group of representatives from national medical device regulatory authorities and the regulated industry. The five founding members were grouped into three geographical areas (Europe, Asia-Pacific, and North America). Over the years, regulatory agencies and medical device trade associations that were not part of the founding members, as well as public health organizations and international standard-setting bodies, were permitted to nominate observers to participate in GHTF study groups and other expert working groups. See International Medical Device Regulators Forum, "GHTF History", online: <www.imdrf.org/ghtf/ghtf-history.asp>; International Medical Device Regulators Forum, "GHTF Roles and Responsibilities", online: <www.imdrf.org/docs/ghtf/final/steering-committee/procedural-docs/ghtf-sc-n2r12-100421-ghtf-roles-and-responsibilities.doc>.

from sometimes debilitating conditions. Many cannot be removed without significant risks of serious morbidity. It is thus pertinent to examine whether existing MD regulations, requirements, and practices are adequately protecting patients from ineffective or potentially hazardous products. As such, we have focused our review on ethical concerns specific to how evidence is collected regarding device safety and performance in research and clinical practice contexts and in premarket and post-market reviews for high-risk MDs.

I. Background

While the MD market is only half the size of the global pharmaceutical market, this sector is growing faster than its drug counterpart.[10] Unlike the drug sector, the device industry is highly fragmented and diversified, mainly composed of small industries (fewer than 50 employees) and a few major manufacturers (e.g., Medtronic, Johnson & Johnson). Most typically specialize in developing niche technologies.[11] In 2012, the global market for devices was valued at US$327.7 billion (CA$334.0 billion), excluding *in vitro* diagnostic devices (e.g., those based on next-generation-sequencing platforms). For example, from 2007 to 2012, Canadian device exports increased from CA$1.7 billion to $1.8 billion,[12] while in the US, exports were valued at more than US$44 billion in 2012, an increase of more than 7% from the previous year.[13] It is anticipated that the global compound annual growth rate could be more than 4.4% between 2011 and 2018, compared to that of the pharmaceutical sector, which is predicted to grow at an annual rate of only 2.5% during the same period.[14] The MD sector is thus an important actor in many national economies. The MD industry continues to be very dynamic and competitive, producing basic supplies as well as

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10 Michael Rosen, "Global Medical Device Market Outperforms Drug Market Growth", *WTN News* (2 June 2008), online: <wtnnews.com/articles/4790/>.

11 Industry Canada, *supra* note 2; SelectUSA, "The Medical Device Industry in the United States", online: <selectusa.commerce.gov/industry-snapshots/medical-device-industry-united-states>.

12 Industry Canada, *supra* note 2.

13 SelectUSA, *supra* note 11.

14 EvaluateMedTech Service, "World Preview 2013, Outlook to 2018: The Future of Medtech", online: <info.evaluategroup.com/rs/evaluatepharmaltd/images/EvaluateMedTech_World_Preview_2013_Outlook_to_2018.pdf>.

highly innovative products that play a vital role in improving patient health through technologically advanced care.

As new MDs prove helpful in treating diseases and disabilities, they may become standard treatments and part of the health care environment, changing medical practice and ideally improving the quality of life of patients, especially those who may be in desperate conditions. Notable examples include stents, defibrillators, orthopaedic prostheses, and functional magnetic resonance imaging (fMRI).[15] Attention to these important benefits must, however, be tempered by the recognition that the integration of innovative and expensive MDs into health care systems also contributes to the problematic growth of overall national health expenditures. For example, it has been estimated that for the US, national spending on MDs in 2009 totalled US$145.6 billion.[16] It is worth noting, though, that in Canada in 2011, per capita medical device expenditure was only half of that in the US (i.e., US$183 in Canada versus US$369 in the US).[17]

II. Regulatory Environment

The main purpose of current regulatory processes for MDs is to ensure access to safe and effective products that can benefit patients, and to ensure that patients have a clear understanding of the potential risks and real benefits that some MDs may pose.[18] The approval of MDs depends

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15 Auditor General of Canada, *2011 Status Report of the Auditor General of Canada to the House of Commons* (Ottawa: Office of the Auditor General of Canada, 2011), ch 6: "Regulating Medical Devices – Health Canada" at 1–2, 5.

16 Gerald Donahoe & Guy King, Advanced Medical Tech Association, "Estimates of Medical Device Spending in the United States" (October 2012) at 14, online: AdvaMed <www.lifechanginginnovation.org/sites/default/files/files/Oct%202012%20King%20Report%20FINAL.pdf>

17 Brett J Skinner, "Medical Devices and Healthcare Costs in Canada and 65 Other Countries, 2006 to 2011", *Canadian Health Policy* (9 May 2013) at 7, online: FDA News <www.fdanews.com/ext/resources/files/archives/0/06/06-13-CanadianSpending.pdf>.

18 Ipsos MORI, *Risks and Benefits of Medicines and Medical Devices – Perceptions, Communication & Regulation: General Public Quantitative Survey* (15 May 2009) at 2, online: UK, Medicines & Healthcare Products Regulatory Agency <www.mhra.gov.uk/home/groups/comms-ic/documents/websiteresources/con052027.pdf>.

essentially on an evaluation of their quality, safety, and effectiveness for a particular application and the risks associated with their use. For example, although they have some side effects, contact lenses do not pose the same risks as hip prostheses or active implantable MDs like deep brain stimulators (DBS). Most devices currently on the market pose minimal or moderate risks. High-risk MDs require particular risk-management procedures in the event of malfunction or serious side effects. As such, there have been calls for more rigorous post-market follow-up due to potentially severe and even irreversible side effects, notwithstanding the fact that many MDs are used as last-resort treatments[19] (e.g., cardioverter defibrillators). Understandably, the approval of MDs is subject to risk-classification regulatory requirements that are modulated according to the particular risks associated with the devices' intended use.

In Canada and the US, drug licensing has existed for almost a century. The Canadian *Food and Drugs Act* was introduced in 1920,[20] thirteen years after the 1906 *US Pure Food and Drug Act*,[21] which was itself then replaced in 1938 by the *Federal Food, Drug, and Cosmetic Act*.[22] But the regulations associated with these laws were specifically focused on addressing drug-related issues. National regulatory requirements specific to MDs would not be addressed until the 1970s. It had by then become obvious that the use of certain devices posed problems for patients (e.g., failures, significant adverse outcomes), making the regulation of MDs a necessity. The US *Federal Food*, *Drug, and Cosmetic Act* was consequently modified by the *Medical Device Amendments of 1976*, which for the first time defined a "medical device," introduced a risk-classification system, and gave the FDA the authority to control the marketing (e.g., bans, recalls, and orders for repair, replacement, or refund) of MDs.[23] In Canada, some of the recommendations in the Lalonde Report, *A New Perspective on the Health*

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19 Kevin L Kilgore, "Introduction and Fundamental Requirements of Neuroprostheses" in Kevin L Kilgore, ed, *Implantable Neuroprostheses for Restoring Function* (Waltham, Mass: Woodhead Publishing, 2015) 3 at 8.

20 SC 1920, c 27.

21 Pub L 59-384, 34 Stat 768 (1906).

22 Pub L 75-717, 52 Stat 2040 (1938) (codified as amended at 21 USC).

23 US, Institute of Medicine of the National Academies, Committee on the Public Health Effectiveness of the FDA 510(k) Clearance Process & Board on Population Health and Public Health Practice, *Medical Devices and the Public's Health: The FDA 510(k) Clearance Process at 35 Years* (Washington, DC:

Table 1. Comparison of standard regulatory assessments for medical devices and pharmaceutical drugs

	Manufacturer	
	Device	**Pharmaceutical**
Filing and review	• Device classification (risk-based) • Device description (design input) • Full technical documentation (device specification, production and process, patent description) • Intended use (label) • Clinical evidence of safety and efficacy (clinical data from *in-vitro*, *in vivo* animal data) ↓ • Protocol clinical review ("first-in-human clinical trials with patients") ↓	• Drug description (medical class – e.g., antidepressant – and active pharmaceutical ingredients) • Drug name and structure (physical and chemical characteristics), and controls manufacturing, information about the drug substance and product. • Intended use (label) • Non-clinical pharmacokinetics, bioavailability, microbiology • Pilot background studies (animals *in vivo*) • General investigation plan (Phase I for safety and dosage, Phase II for effectiveness and side effects, Phase III for safety and efficacy) ↓
Trials	• New trials (randomized/placebo) ↓	• Phases I, II, III trials (randomized/placebo trials) ↓
Approval	• For market launch (or re-examination filing) timeline: ≤ 2 years ↓	• For market launch (or amended application) timeline: ≤ 5-10 years ↓
Post-market	• Studies (real-world practice)	• Phase IV studies (real-world practice)

Regulator	
Device	**Pharmaceutical**
• Device classification validation • Design validation (production, manufacturing) • Audit/inspection • Studies/statistical findings to prove or not prove efficacy for intended use ↓ • Process review and validation (device achieves performance for intended use), or • Request for new trials (±100 patient volunteers) ↓	• Drug validation ↓ • Design (production, manufacturing) • Audit/inspection • Study hypotheses/statistical findings prove (or do not prove) efficacy for intended use ↓
• First-in-human clinical trials authorization (± 20 patient volunteers) ↓ • Request for new trials (±100 patient volunteers) ↓	• Phase I clinical trials authorization (>100 healthy volunteer subjects) ↓ • Process review and validation (drug achieves performance for intended use) ↓ • Phase II clinical trials authorization (100–500 patient volunteer subjects) ↓ • Process review and validation (drug achieves performance for intended use) ↓ • Phase III clinical trials authorization (1000–5000 patient volunteers) ↓
• For intended use (or denied) ↓	• For intended use (or denied) ↓
• Manufacturers' reporting ↓ • Recalls, advertisements, bans	• Manufacturers' reporting ↓ • Warnings, recalls, bans

of Canadians: A Working Document,[24] called for increasing controls over MDs because many could be considered "hazardous products" for health. In 1975, amendments to the Canadian *Food and Drugs Act* introduced strict requirements and guidelines to regulate the licensing of MDs.[25] Yet, unlike in the US, in Canada a risk-classification system would only be introduced in 1998. Similarly, in Australia, Japan, and the EU, formal MD regulations were introduced in the 1990s. Table 1 shows key similarities and differences between the device and drug sectors with regard to the premarket evaluation process and the follow-up by regulators and manufacturers after a drug or MD has been approved for marketing.

In 1992, the regulatory authorities of five national systems (Australia, Canada, the EU, Japan, and the US) established the Global Harmonization Task Force (GHTF) to stimulate convergence and ideally the harmonization of standards and regulatory practices concerning the safety, performance, and quality of MDs. To this end, the GHTF developed numerous guidance documents that could be of benefit to any country seeking to improve its MD regulations (providing, for example, a definition of "medical device," guidance about premarket evaluation and post-market surveillance, and procedures for auditing of quality management).[26] In April 2012, the GHTF was dissolved and replaced by the International Medical Device Regulators Forum, whose Management Committee is composed exclusively of regulatory officials from Australia, Brazil, Canada, China, Europe, Japan, Russia, and the US. Through working groups, this Committee will profit from the expertise of the industry, academia, health care professionals, and consumer and patient groups.[27]

National Academies Press, 2011) at 1–2; *Medical Device Amendments of 1976*, Pub L No 94-295, 90 Stat 539.

24 Marc Lalonde, Minister of National Health and Welfare, *A New Perspective on the Health of Canadians: A Working Document* (1974) (reissued: Ottawa: Minister of Supply and Services Canada, 1981) at 47, 69.

25 *Regulations respecting Medical Devices*, SOR/75-526; US, Congress, Office of Technology Assessment, *Federal Policies and the Medical Devices Industry* (Washington: US Government Printing Office, 1984).

26 Major guidance documents generated by the GHTF, especially about classification and premarket and post-market evaluation principles, can be found on the International Medical Device Regulators Forum website. See "GHTF Archived Documents" (nd), *International Medical Device Regulators Forum*, online: <www.imdrf.org/ghtf/ghtf-archived-docs.asp>.

27 The current organization of the International Medical Device Regulators

We have based our review on the current national regulatory processes of the five former GHTF founding members, because under the GHTF's initiative, significant progress has been made towards international harmonization in the regulation of MDs, especially with regard to registration and approval requirements. Table 2 presents a summary of the requirements for MD assessment and approval as set forth by government authorities. The regulatory environment of MDs is evolving rapidly and other changes are likely to be introduced in the coming months. For example, an amendment to the Canadian *Food and Drugs Act* – Bill C-17, *Protecting Canadians from Unsafe Drugs Act (Vanessa's Law)*[28] – was adopted in 2014; this law introduced innovative measures to reinforce post-market regulatory activities for both drugs and MDs.[29]

Despite the success of the GHTF in harmonizing national regulatory requirements, there has been a notable increase in alerts and recalls of high-risk MDs in recent years, particularly in the US and in Europe. For example, Heneghan and colleagues reported that between 2006 and 2010, there was a 1220% increase in the number of safety notices issued in the United Kingdom (62 in 2006 versus 757 in 2010), nearly half of which concerned high-risk MDs with a probability of causing serious adverse health consequences.[30] There are thus still serious problems with national regulatory review of MDs, both in premarket assessment and evaluation and in post-market surveillance.

Forum can be found online. See "About IMDRF", *International Medical Device Regulators Forum*, online: <www.imdrf.org/about/about.asp>.

28 Bill C-17, *An Act to amend the Food and Drugs Act*, 2nd Sess, 41st Parl, 2014 (assented to 6 November 2014), SC 2014, c 24 [Bill C-17]. See also Health Canada, "Protecting Canadians from Unsafe Drugs Act (Vanessa's Law)/ Amendments to the *Food and Drugs Act* (Bill C-17)" (last updated 31 July 2015), online: <www.hc-sc.gc.ca/dhp-mps/legislation/unsafedrugs-drogues-dangereuses-eng.php>. *Vanessa's Law* is named after the daughter of Terence Young, a Member of Parliament, who died of a heart attack while she was on a prescription drug that was later removed from the market.

29 A previous attempt to amend the *Food and Drugs Act* made it to second reading in the House of Commons in 2008. See Bill C-51, *An Act to amend the Food and Drugs Act and to make consequential amendments to other Acts*, 2nd Sess, 39th Parl, 2008 [Bill C-51].

30 Carl Heneghan et al, "Medical-Device Recalls in the UK and the Device-Regulation Process: Retrospective Review of Safety Notices and Alerts", online: (2011) 1:1 Brit Med J Open e000155.

Table 2. Regulatory systems of GHTF founding members†

	Australia	Canada
Legislation	• *Therapeutic Goods Act* (1989) • *Therapeutic Goods Regulations* (1990) • *Therapeutic Goods (Medical Devices) Regulations* (2002)	• *Food and Drugs Act* (RSC 1985) • *Medical Devices Regulations* (1998) • *Protecting Canadians from Unsafe Drugs Act* (2014)
Governance	• Department of Health and Ageing • Therapeutic Goods Administration	• Health Canada • Therapeutic Products Directorate
Device classification	• Class I • Class IIa • Class IIb • Class III • Special Class III (AIMD)	• Class I • Class II • Class III • Class IV
Medical device regulations	• Introduced 1990 • Revised 2002 • 2013 (under review)	• Introduced 1975 • Revised 1998
Pre-approval clinical regulatory requirements	• Quality, safety, and efficacy assessment • Compilation of quality management system design for Class III and AIMD	• Risk assessment for Class IV • Investigational testing authorization (new device) • Emergency use program (unapproved device) • FDA guidance may be used by Health Canada
Post-market structure requirements	• Comprehensive vigilance system • Post-market surveillance reports • Unique device identifier (implantable devices)	• MedEffect • *Protecting Canadians from Unsafe Drugs Act*

† Table sources are provided in the Appendix.

EU	Japan	United States
• Council directives 90-385 EEC, 93/42 EEC, 98/79 EEC, 2007/47/EEC	• *Pharmaceutical Affairs Law* (2005) • *Pharmaceutical Affairs Law* (2013) (name changed to *Act on Securing Quality, Efficacy and Safety of Pharmaceuticals, Medical Devices, Regenerative and Cellular Therapy Products, Gene Therapy Products, and Cosmetic* (2014))	• *Medical Device Amendments* (1976) • *Safe Medical Devices Act of 1990* • *Food and Drug Administration Modernization Act of 1997* • *Food and Drug Administration Safety and Innovation Act* (2012)
• European Commission • Laws of the Member States • Notified Bodies	• Ministry of Health, Labour and Welfare • Pharmaceuticals and Medical Devices Agency	• Food and Drug Administration • Center for Devices and Radiological Health
• Class I • Class IIa • Class IIb • Class III • Special Class III (AIMD)	• Class I • Class II (specified control) • Class II (controlled) • Class III • Class IV (specially controlled MD)	• Class I • Class II • Class III
• Introduced 1993 • Revised 2007, 2010, 2012 • 2014 (under review)	• Introduced 1995 • Revised 1997, 2004, 2013, 2014	• Introduced 1976 • Revised in 1997, 2013
• Safety assessment • Clinical trials: mandatory for Class III, AIMD, and long-term-use invasive devices • Most trials: non-randomized and single arm (aim at providing safety)	• Japanese GCP regulations • Clinical risk assessment • Foreign clinical data accepted • Premarket certification (Class IIa) • Premarket approval (classes IIb, III, and IV)	• Mandatory clinical trials for Class III • Premarket approval (PMA) • Premarket notification (510k) • Humanitarian device exemption • *De novo* process • Investigational device exemption (new device and use) • Clinical data are treated as trade secrets
• Vigilance system • Unique device identifier • CE conformity approval • EUDAMED (non-public database) • Unique device identifier (implantable devices)	• Follow-up evaluations • Medical Information for Risk Assessment Initiative Project for implantable devices (MIHARI) • Japanese registry for mechanically assisted circulatory support (J-MACS)	• Post-market Transformation Initiative • Sentinel Initiative • MAUDE • MedWatch • Unique device identifier (implantable devices)

III. Premarket Risk Assessment

To evaluate devices before they enter the market, the GHTF founding members' national MD processes have adopted a risk-classification approach based on the intended purpose and use of each MD, its potential hazards, and the appropriate controls that need to be implemented to ensure its safety and effectiveness.[31] It is understandable that low-risk devices such as bandages and examination gloves would easily obtain clearance before being approved for market, and, in order to speed patient access to such low-risk MDs, some may even be exempted from premarket review. But these low-risk devices are still subject to post-market oversight (i.e., good manufacturing requirements, factory inspections) because they are not free from potential malfunctions or adverse events. On the other hand, high-risk MDs such as orthopaedic implants, pacemakers, and brain stimulators clearly require much closer scrutiny, and their manufacturers must provide "reasonable" evidence of their products' safety and effectiveness.

When filing an application for a licence to market medium- and high-risk devices, manufacturers are normally required to demonstrate that they meet internationally accepted standards in the design and manufacturing of their MDs, i.e., ISO international standards.[32] To be approved, a MD should satisfy specific requirements with regard to potential risks defined according to their severity, ranging from negligible (hence acceptable) and marginal to critical or catastrophic (and thus intolerable) for a patient's health or life. This classification system is based on a series of factors, including how long the device is intended to be in continuous use, the duration of contact in or on the affected body part, whether or not the device is invasive or requires surgical intervention, and whether the device is active or non-active im-

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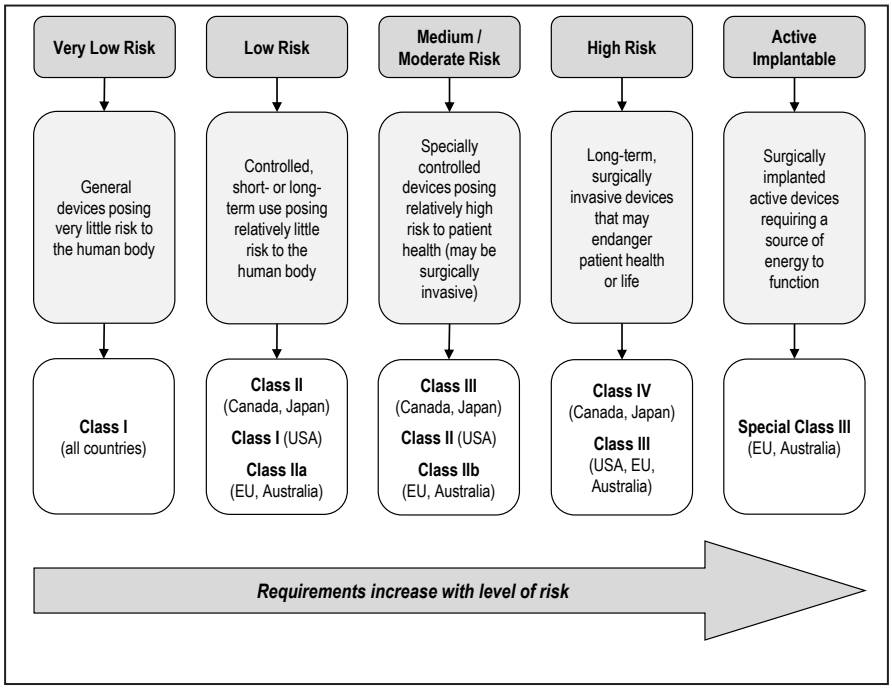
31 See Table 2, above.

32 Most countries recognize the ISO standards. The US FDA does not, and instead follows its own system, although it has many overlapping elements with the ISO standards. See Judith A Johnson, "FDA Regulation of Medical Devices", Congressional Research Service [CRS] Report for Congress (25 June 2012), online: Federation of American Scientists <www.fas.org/sgp/crs/misc/R42130.pdf>; "ISO 13485, 60601 and Other Standards that Apply to the Medical Device Industry" (nd), *Emergo Group*, online: <www.emergogroup.com/resources/articles/use-of-standards>; World Health Organization, *Medical Device Regulations: Global Overview and Guiding Principles* by Michael Cheng (Geneva: WHO, 2003) at 13, online: <www.who.int/medical_devices/publications/en/MD_Regulations.pdf> [World Health Organization, *Medical Device Regulations*].

FIGURE 1. MEDICAL DEVICE CLASSIFICATION



plantable. Figure 1 summarizes the main MD specifications used in national classification systems.

In principle, harmonization should facilitate the development of international best practices that ensure the safety and effectiveness of MDs before and after entering the market, namely through standards regarding how clinical evidence is reported and examined, including clinical-trial registration and the public release of results.[33] Such initiatives should not be limited to classification or be simply a matter of assisting manufacturers in filing documents across regulatory authorities, nor should they be a means to eliminate trade barriers for the device industry or to reduce the time to

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[33] Joel Lexchin, "Who's Calling the Tune: Harmonization of Drug Regulation in Canada", Canadian Centre for Policy Alternatives (January 2011) at 5, 11–14, online: <www.policyalternatives.ca/sites/default/files/uploads/publications/National%20Office/2011/01/Whos%20Calling%20the%20Tune.pdf> [Lexchin, "Harmonization of Drug Regulation"].

market for a device.[34] As is the case for pharmaceutical drugs, regulatory harmonization is a means of protecting public health.[35]

Unfortunately, current national systems are still not fully harmonized across the GHTF founding members, and many weaknesses remain in their control of medium- to high-risk MDs. In premarket review in the US, for example, clinical assessment of MDs is based on "reasonable assurance of safety and effectiveness,"[36] meaning that the assessment is less demanding than for drugs, provided the anticipated benefits outweigh the risks associated with their use. By comparison, pharmaceutical drugs are required to show "substantial evidence" of effectiveness to obtain approval.[37] The same situation is observed in Europe, where the premarket clinical assessment for high-risk MDs is not comparable to that for pharmaceutical drugs because clinical efficacy is usually not part of premarket assessment for MDs.[38]

It is estimated that high-risk MDs account for less than 5% of the many thousands of medical devices on the market internationally. In the US, out of the 8,000 new MDs marketed each year, only 50 to 80 are Class III, the US class designating high-risk MDs.[39] Similarly, in its last regulatory review of performance for pharmaceuticals, biologics, and MDs, Health Canada reported that out of the 4,896 MD applications, only 112 involved Class IV

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34 Susan Lamph, "Regulation of Medical Devices outside the European Union" (2012) 105:1 (supp) J Roy Soc Med S12 at S13; A Kaushik et al, "Harmonized Medical Device Regulation: Need, Challenges, and Risks of Not Harmonizing the Regulation in Asia" (2010) 2:1 J Young Pharm 101 at 104.

35 Lexchin, "Harmonization of Drug Regulation", *supra* note 33 at 14.

36 *Food, Drug, and Cosmetics Act*, 21 USC § 360c.

37 Sweet, Schwemm & Parsons, *supra* note 4 at 43; Jonas Zajac Hines et al, "Left to Their Own Devices: Breakdowns in United States Medical Device Premarket Review", online: (2010) 7:7 PLoS Med e1000280 at 6 <www.plosmedicine.org/article/fetchObject.action?uri=info:doi/10.1371/journal.pmed.1000280&representation=PDF>.

38 Frank Hulstaert et al, "Premarket Clinical Evaluations of Innovative High-Risk Medical Devices in Europe" (2012) 28:3 Int J Technol Assess Health Care 278 at 280.

39 Sanket S Dhruva, Lisa A Bero & Rita F Redberg, "Strength of Study Evidence Examined by the FDA in Premarket Approval of Cardiovascular Devices" (2009) 302:24 JAMA 2679 at 2679 [Dhruva, Bero & Redberg, "Strength of Study Evidence"].

(i.e., Canadian high-risk) devices.[40] Nonetheless, while they may represent a small percentage of all the MDs on the market, high-risk MDs are very often used in treatments of last resort, and therefore any failure on the part of regulatory evaluation and oversight can have a significant impact on patients (and on health expenditures) and potentially undermine the public's confidence in regulatory authorities.

A. Challenging issues in US regulation: The 510(k) expedited review process

One aspect of MD regulation that is unique to the US and that merits particular attention is the so-called "510(k) expedited premarket review process" (named after a federal law passed in 1976 and amended in 1990 and 1997).[41] Many in the medical and scientific communities have criticized this "fast-track approval" of MDs because of the numerous problems (i.e., failures and recalls) encountered over the past several years related to devices approved under this process.

Manufacturers filing through the 510(k) process do not have to provide proof of safety and effectiveness data for human use if they claim that a device is "substantially equivalent" to an already approved device, which is called the "predicate." This process was originally intended for medium-risk MDs; but over the years, many high-risk devices have also been approved under this process, when in fact they should have gone through the more stringent Premarket Approval (PMA) Application (see Table 3). A 510(k) clearance requires manufacturers to notify the FDA 90 days in advance of an intention to market a new product that is substantially equivalent to an already approved predicate device.[42] Not only does the 510(k) process make

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40 Health Canada, *Regulatory Review of Pharmaceuticals, Biologics and Medical Devices: 2005 Annual Summary of Performance* (2006) at 8, online: <www.hc-sc.gc.ca/ahc-asc/alt_formats/hpfb-dgpsa/pdf/pubs/performance_rendement_2005-eng.pdf>.

41 See Sweet, Schwemm & Parsons, *supra* note 4 at 41–42; "A Brief History of US Medical Device Regulation" (nd), *Emergo Group*, online: <www.emergogroup.com/resources/history-us-medical-device-regulation>.

42 See Kathleen Blake, "Postmarket Surveillance of Medical Devices: Current Capabilities and Future Opportunities" (2012) 36:2 J Interv Card Electrophysiol 119 at 120.

Table 3. Premarket FDA ruling concerning approval process

Premarket Notification under 510(k)	Premarket Approval (PMA) Application
• Submitted to the FDA by the device sponsor/manufacturer 90 days before marketing commences for any Class I or Class II device intended for human use for which a PMA is not required • Most Class I devices are exempt from the 510(k) requirement • May be filed by sponsor/manufacturer for a Class III device, provided that the device is claimed to be at least as safe and effective as a substantially equivalent device that is legally marketed (the "predicate") – that is, if it has the same intended use and the same technological characteristics or different characteristics that do not raise new questions about safety and effectiveness, and if the sponsor demonstrates that the device is at least as safe and effective as the legally marketed device • Substantial equivalence does not mean the new and predicate devices must be identical; this is established according to intended use, design, energy used or delivered, materials, chemical composition, manufacturing process, performance, safety, effectiveness, and labelling • Review timeframe: 3–5 months	• The most stringent type of device marketing application required by the FDA; for Class III devices (high-risk) involving any new concept or innovative technology for which there is no predicate, i.e., for which there is no substantially equivalent legally marketed device, or no substantially equivalent Class I or Class II device • Applicants are usually the persons (entities) who own the rights, or otherwise have authorized access, to the data and other information to be submitted in support of FDA approval • A complete set of design control documents are expected as part of the PMA submission, e.g., summary of safety and effectiveness, non-clinical and clinical data, risk assessment, quality plan, device-specific detailed information, manufacturing methods, labelling information, quality system requirements • Device is evaluated according to sufficient valid scientific evidence to assure safety and effectiveness for its intended use, i.e., involving well-controlled investigations for the targeted population • Manufacturers should perform quality control audits • Review timeframe: 12–24 months

Sources: US, Food and Drug Administration, "Premarket Notification 510(k)" (last updated 16 September 2015), online: <www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/HowtoMarketYourDevice/PremarketSubmissions/PremarketNotification510k>; US, Food and Drug Administration, "PMA Review Process" (26 March 2015), online: <www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/HowtoMarketYourDevice/PremarketSubmissions/PremarketApprovalPMA/ucm047991.htm>.

it easier for manufacturers to obtain approval for a new device, but it is also less expensive. As of 30 September 2015, premarket notification fees under 510(k) were US$5,228 (standard fee) or US$2,614 (for small businesses), while for the more rigorous PMA Application, fees were US$261,388 (standard fee) or US$65,347 (for small businesses).[43]

Numerous high-risk MDs have been approved through the 510(k) clearance process.[44] Between 2003 and 2007, up to 228 high-risk MDs obtained FDA approval without a close scientific review, i.e., without providing any appropriate clinical data or any data at all.[45] A study by Zuckerman and colleagues found that 71% of the high-risk devices recalled in the US between 2005 and 2009 were given market approval through the 510(k) process. Recalled devices included cardiovascular, intravenous infusion, anaesthesiological, and neurological devices.[46] In one striking example, Medtronic's Sprint Fidelis Leads – cardiac electrodes for implantable defibrillators – were approved by the FDA in 2004 without any premarket clinical testing and were then recalled in 2011 because the leads could fracture, resulting in serious injuries and even some deaths.[47] Another example is the Birmingham hip, an all-metal hip replacement that Johnson & Johnson's DePuy Orthopaedics claimed was substantially equivalent to other models and so received clearance in the US for marketing without conducting formal clinical trials

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43 US, Food and Drug Administration, *FY 2016 Medical Device User Fee – Small Business Qualification and Certification; Guidance for Industry, Food and Drug Administration Staff and Foreign Governments* (3 August 2015), online: <www.fda.gov/ucm/groups/fdagov-public/@fdagov-meddev-gen/documents/document/ucm456779.pdf>.

44 See Carlos Campillo-Artero, "A Full-Fledged Overhaul Is Needed for a Risk and Value-Based Regulation of Medical Devices in Europe" (2013) 113:1–2 Health Policy 38 at 40.

45 See US, Government Accountability Office, *Medical Devices: FDA Should Take Steps to Ensure that High-Risk Device Types Are Approved through the Most Stringent Premarket Review Process* (GAO-09-190) (January 2009) at 16, online: <www.gao.gov/new.items/d09190.pdf>.

46 Diane M Zuckerman, Paul Brown & Steven E Nissen, "Medical Device Recalls and the FDA Approval Process" (2011) 171:11 Arch Intern Med 1006 at 1008.

47 See Rita F Redberg & Sanket S Dhruva, "Medical Device Recalls: Get It Right the First Time" (2011) 171:11 Arch Intern Med 1011 at 1011.

to demonstrate safety and efficacy.[48] After thousands of complaints and lawsuits due to device failures, and after having been implanted in almost 100,000 people worldwide, the device was recalled in 2010 in the UK.[49]

Cardiovascular devices were among those MDs most often recalled, with one study showing that between 2000 and 2007, 65% of such devices were approved after only a single clinical trial.[50] Another study showed that most high-risk cardiovascular devices were approved in the US without presentation of comparative effectiveness data.[51] Among the 123 studies used to support FDA approval of cardiovascular devices in the US between 2000 and 2007, fewer than a third were randomized controlled trials.[52] Further, a study by Boudard and colleagues revealed that more than half of 215 studies seeking to quantify the level of evidence available for innovative MDs included fewer than 30 patients.[53]

In the face of the numerous recalls of high-risk MDs, the US Institute of Medicine advocated for the elimination of the 510(k) process, while Zuckerman and colleagues called on the FDA to strengthen its authority to use the same special controls for 510(k) devices as they use for PMA

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48 See Carl Heneghan, David Langton & Matthew Thompson, "Ongoing Problems with Metal-on-Metal Hip Implants" (2012) 344 Br Med J e1349 at 2.

49 See Matthias Wienroth et al, "Precaution, Governance and the Failure of Medical Implants: The ASR™ hip in the UK" (2014) 10:19 Life Sci Soc Policy 1 at 1. Also, a study published in 2012 reported that 31,172 hip replacements (out of 402,051) undertaken between 2003 and 2011 were stemmed metal-on-metal; see Alison J Smith et al, "Failure Rates of Stemmed Metal-On-Metal Hip Replacements: Analysis of Data from the National Joint Registry of England and Wales" (2012) 379:9822 Lancet 1199 at 1199.

50 See Dhruva, Bero & Redberg, "Strength of Study Evidence", *supra* note 39 at 2680.

51 See Connie E Chen, Sanket S Dhruva & Rita F Redberg, "Research Letter: Inclusion of Comparative Effectiveness Data in High-Risk Cardiovascular Device Studies at the Time of Premarket Approval" (2012) 308:17 JAMA 1740 at 1742.

52 See Dhruva, Bero & Redberg, "Strength of Study Evidence", *supra* note 39 at 2680.

53 Aurélie Boudard et al, "Clinical Studies of Innovative Medical Devices: What Level of Evidence for Hospital-Based Health Technology Assessment?" (2013) 19:4 J Eval Clin Prac 697 at 701.

devices.[54] In response to these and other critiques,[55] the FDA launched a review of the 510(k) process to make it more effective and to ensure the enforcement of the review standards, particularly for high-risk MDs. In August 2012, the FDA released a draft 510(k) guidance document, the *Refuse to Accept Policy for 510(k)s* (followed by a formal release in December that year),[56] to clarify current premarket notification practices. The goal was to assist device manufacturers to better understand (through checklists) which types of information the FDA needs to conduct a thorough review of a new device or a new intended use of a device, prior to its being considered for a more substantive review, especially when the new device is claimed to be "substantially equivalent" to a predicate. Later, the FDA published guidance to improve device review practices[57] to fulfill commitments announced in 2011 in the Center for Devices and Radiological Health (CDRH)'s *Plan of Action*;[58] some of these commitments address the quality and consistency of review standards of 510(k) applications. Initiatives were announced to improve guidance and training for reviewers and industry on the standards and to clarify the clinical/technical data requirements for approval and clearance under 510(k) in order to address misunderstandings of the standards for clearance (e.g., definition of a "substantially equivalent device," "intended use" versus "indications for use," and the types of clinical and technical data to be provided).

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54 US, Institute of Medicine of the National Academies, *supra* note 23 at 3; Zuckerman, Brown & Nissen, *supra* note 46 at 1010.

55 Redberg & Dhruva, *supra* note 47.

56 The latest version is US, Food and Drug Administration, Center for Devices and Radiological Health & Center for Biologics Evaluation and Research, *Refuse to Accept Policy for 510(k)s: Guidance for Industry and Food and Drug Administration Staff* (4 August 2015), online: <www.fda.gov/downloads/medicaldevices/deviceregulationandguidance/guidancedocuments/ucm315014.pdf>.

57 *Proposed Rule: Unique Device Identification System*, 77 Fed Reg 40736 (2012). For the final rule as adopted, see 78 Fed Reg 58786 (2013) (codified at 21 CFR Parts 16, 801, 803, 806, 810, 814, 820, 821, 822, and 830) [FDA, *Final UDI Rule*].

58 The latest update on the implementation of the *Plan of Action* is US, Food and Drug Administration, Center for Devices and Radiological Health, *CDRH Plan of Action for 510(k) and Science* (May 2014) at 4, online: <www.fda.gov/downloads/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDRH/CDRHReports/UCM297583.pdf>. The original 2011 version is available at <www.fda.gov/downloads/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDRH/CDRHReports/UCM239450.pdf>.

B. Adaptive licensing: A better approach for high-risk MDs?

The particularities of the 510(k) process are specific to the US device regulation regime. None of the other GHTF member countries have anything equivalent. Nor is the implementation of such a process on their agenda, even in the long-term. Nonetheless, there are other approaches that could potentially speed up the approval process of high-risk devices while still guaranteeing safety and effectiveness. Specifically, some form of "conditional approval" could be a promising approach to facilitate early access within current regulatory frameworks but without compromising patient safety.

Health Canada started along the path to implementing just such an initiative in 2007, when it announced that it had developed a framework to improve the regulation of drugs (the "Progressive Licensing Model") by providing guidance regarding regulatory requirements for premarket pharmacovigilance and therapeutic effectiveness management.[59] Although no mention was made at the time about expanding this to MDs, existing problems with the approval of high-risk MDs certainly provide grounds for justifying such an extension. To improve post-market surveillance practices for the sale or use of any "therapeutic product," in 2008 the Canadian government introduced Bill C-51, an amendment to the *Food and Drugs Act*, which had a particular focus on regulating natural health products and promoted a "life cycle" regulatory approach for all health products (including drugs).[60] Because of controversy about this proposed legislation, the bill was never adopted. Health Canada chose instead to move on to enforcing measures at the post-market surveillance level for all therapeutic products, including MDs, through Bill C-17, *Vanessa's Law*, which received Royal Assent on 6 November 2014.[61] The many amendments that this law brings to the

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59 Neil Yeates, David K Lee & Maurica Maher, "Health Canada's Progressive Licensing Framework" (2007) 176:13 CMAJ 1845; Health Canada, "Progressive Licensing Model" (last updated 19 September 2007), online: <www.hc-sc.gc.ca/dhp-mps/homologation-licensing/model/index-eng.php>.

60 Bill C-51, *supra* note 29; Marlisa Tiedemann, Law and Government Division, Parliamentary Information and Research Service, "Bill C-51: An Act to Amend the Food and Drugs Act and to Make Consequential Amendments to Other Acts", Legislative Summary LS602E (revised 24 July 2008) at 2, Library of Parliament, online: <www.parl.gc.ca/Content/LOP/LegislativeSummaries/39/2/c51-e.pdf>.

61 *Supra* note 28.

Canadian *Food and Drugs Act* will enable Canada to implement what we consider an optimal post-market surveillance strategy, instead of the current "wait and see" approach that relies on adverse-event reporting (discussed in more detail in Part VI below).

Representatives of the FDA and the European Medicines Agency (EMA) have discussed the opportunity to adopt an approach based on a provisional approval concept (or conditional marketing authorization), referred to as "adaptive licensing."[62] The intent of such a process is to enable better-informed decisions based on iterative phases of data gathering and marketing authorizations throughout the drug development process. A corresponding approach could be extended to MDs, but however promising this might be, it will still meet numerous challenges. Prime among these challenges is the need for the key stakeholders (i.e., regulators, industry, payers, and health care providers) to openly share information regarding safety and efficacy data along with the potential economic impact of MD reimbursement rates. This information is essential for effective HTA and decision making by third-party payers in order to avoid the perception that adaptive licensing means lower standards of efficacy, safety, and/or quality of a device.[63] Further, the very specific development path of MDs – i.e., the iterative process based on constant R&D in close relation with clinical practice, the reactivity to other scientific advances (e.g., new materials, advanced engineering), and the short product life cycles – can raise additional challenges with regard to both off-label use (when and under what conditions is this ethically permissible?) and the term and duration of patents and exclusivity periods.[64] As such, adaptive licensing may constitute a promising and flexible approach to integrating potentially beneficial but still risky MDs into health care provision, while also addressing the pricing and conditions for reimbursements – important issues for third-party payers, clinicians, and patients.

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62 See H-G Eichler et al, "Adaptive Licensing: Taking the Next Step in the Evolution of Drug Approval" (2012) 91:3 Clin Phamacol Ther 426; Kenneth Oye et al, "Legal Foundations of Adaptive Licensing" (2013) 94:4 Clin Phamacol Ther 309 [Eichler et al, "Adaptive Licensing"].

63 Jasmina Savic, "Adaptive Licensing: A Solution to the Market Access vs Evidence Dilemma?" (14 August 2013), *Pharmaceutical Compliance Monitor*, online: <www.pharmacompliancemonitor.com/adaptive-licensing-a-solution-to-the-market-access-vs-evidence-dilemma/5390/>; Eichler et al, "Adaptive Licensing", *supra* note 62 at 434.

64 Eichler et al, "Adaptive Licensing", *supra* note 62 at 435.

But attention must also be given to implementing measures to educate health care providers and the public so that they understand the inherent uncertainties that will remain with regard to any MDs approved through adaptive licensing. For example, there might be uncertainties about health benefits or unforeseen risks, or even regarding which MDs are eligible for reimbursement (although many patients with serious life-threatening conditions may be less risk-averse than regulators).[65] Further, the ongoing collection of evidence by regulators and HTA agencies could be challenging. Interestingly, the EMA recently announced that it had selected six drugs to move forward in the Adaptive Pathways Pilot Program, launched in March 2014. This program involves collaboration among a wide range of stakeholders: regulators, the pharmaceutical industry, HTA agencies, organizations issuing clinical treatment guidelines, patient and consumer organizations, health care professionals, researchers, and academics.[66]

The challenge, then, is striking a realistic balance between, on the one hand, patient hopes and interests in benefiting from a new or still conditionally approved "experimental" MD and, on the other hand, a fair evaluation of the risks that remain to be documented and are associated with its use in the health care system. A further problem is preventing undue influence on patients (e.g., by clinicians or manufacturers) and therapeutic misconception.[67] Attention paid by clinician-researchers to core ethical principles, such as beneficence/non-maleficence and respect for patient autonomy, can help ground a healthy therapeutic alliance between themselves and their patients so that patient goals, experiences, and preferences are weighed appropriately against the potential risks and benefits associated with the intervention and its follow-up, especially when clinical safety and efficacy have not yet been demonstrated.[68]

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65 *Ibid* at 428–29.

66 European Medicines Agency, "Adaptive Pathways" (nd), online: <www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general_content_000601.jsp>.

67 See e.g. Gail E Henderson et al, "Clinical Trials and Medical Care: Defining the Therapeutic Misconception", online: (2007) 4:11 PLoS Med 1735 <www.plosmedicine.org/article/fetchObject.action?uri=info:doi/10.1371/journal.pmed.0040324&representation=PDF>; Charles W Lidz & Paul S Appelbaum, "The Therapeutic Misconception: Problems and Solutions" (2002) 40:9 (supp) Med Care V-55.

68 Courtenay R Bruce, "A Review of Ethical Considerations for Ventricular As-

C. *Other national regulatory improvements*

1. The European Union

In September 2012, following harsh criticisms of its existing process, the European Commission (EC) adopted a proposal for significant amendments to the regulatory framework concerning the approval of MDs, particularly with regard to traceability, safety, clinical performance, and active implantable devices.[69] The proposed EC regulations (as opposed to directives) would shift European practice to a "premarket authorization" approach in order to better examine uncertainties and ensure transparency (e.g., through a central registry for clinical studies) and traceability (e.g., through unique device identification). The regulations would apply to certain, mostly high-risk MDs, including implants and other invasive products used for cosmetic purposes, and products that do not serve a medical purpose, such as non-corrective contact lenses. The new rules still remain to be endorsed by the European Union's 28 member states before they can become law.[70] Although the law was originally expected to be adopted in 2014 and implemented between 2015 and 2018, it was only in June 2015 that the Council of Ministers of the European Union decided on a "general approach" for the new regulations. Yet the Council of Ministers confirmed that a mandate has been given for its Luxembourg presidency to open "trilogue" talks with the European Parliament and European Commission on the planned new regulations.[71]

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sist Device Placement in Older Adults" (2013) 4:2 Aging Dis 100 at 104; Hulstaert et al, *supra* note 38.

69 EC, *Proposal for a Regulation of the European Parliament and of the Council on medical devices, and amending Directive 2001/83/EC, Regulation (EC) No 178/2002 and Regulation (EC) No 1223/2009*, COM(2012) final 542, 2012/0266 (COD) (26 September 2012).

70 For the legislative history of the proposal, see EUR-Lex, "Procedure 2012/0266/COD" (last updated 5 October 2015), online: <eur-lex.europa.eu/procedure/EN/201998>.

71 Ronald Boumans, "Negotiating New Regulations for Medical Devices and IVDs in Europe" (June 2015), *Emergo Group*, online: <www.emergogroup.com/blog/2015/08/negotiating-new-regulations-medical-devices-and-ivds-europe>; "Final Negotiations Set to Begin on New EU Medical Device regulations" (25 September 2015), online: <www.out-law.com/en/articles/2015/september/final-negotiations-set-to-begin-on-new-eu-medical-device-regulations/>.

Eucomed,[72] an industry association representing the European medical technology industry in Europe, fought this reform, claiming that it would kill innovation, and so asked for substantial modifications.[73] The European Commission has nonetheless kept its focus on toughening current requirements (especially for the high-risk class) to ensure that MDs undergo more stringent safety and efficacy assessment by Special Notified Bodies.[74] In September 2013, the European Parliament's Committee on the Environment, Public Health and Food Safety (ENVI) voted in favour of a new and more stringent regulatory framework that would require some devices to go through a premarket assessment process with the EMA. Based on what is currently the norm in drug development, one measure being promoted in the EU at the level of premarket safety and effectiveness assessment is the "adaptive design" of early-phase clinical studies. Under this approach, and based on accumulated data, pre-specified modifications (e.g., to the number of subjects, endpoints, trial duration, and/or patient population) are allowed during the course of a trial. According to Mahajan and Gupta, this path would not compromise the validity and integrity of the trials.[75] The purpose of such an approach is to allow researchers to modify or redesign a trial while it is still ongoing.[76]

Despite the many benefits of adaptive design, some argue that significant ethical concerns need to be considered, including the loss of clinical

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[72] The Eucomed website has recently been incorporated into the MedTechEurope platform, an alliance of European medical technology industry associations founded by EDMA, which represents the European *in vitro* diagnostic industry.

[73] Eucomed, *Towards a Regulation that Guarantees Patient Safety, Ensures Patient Access and Keeps Innovation in Europe: Eucomed's Response to the Commission's Proposal for the Revision of the EU Medical Devices Directives*, Position Paper (30 January 2013), online: <www.medtecheurope.org/node/487>.

[74] Special Notified Bodies (SNBs) are Notified Bodies (NBs) with specific expertise that will be designated to evaluate high-risk (Class III and active implantable) MDs and any novel technologies. Only those will be entitled to conduct conformity assessments. See "New Medical Device Regulation: Introducing Special Notified Bodies" (3 March 014), *Medical Device Plus*, online: <www.ceplus.eu/index.php?id=6137&setlang=EN>.

[75] Rajiv Mahajan & Kapil Gupta, "Adaptive Design Clinical Trials: Methodology, Challenges and Prospect" (2010) 42:4 Indian J Pharmacol 201 at 201.

[76] Shein-Chung Chow, "Adaptive Clinical Trial Design" (2014) 65 Annu Rev Med 405 at 406.

equipoise, the lack of processes for adequate informed consent, and conflict between research and clinical care goals.[77] Current practices for high-risk devices, at both the premarket and post-market levels, raise major ethical issues, primary among which are the guidelines associated with patient selection and informed consent. For instance, in premarket clinical trials, the patients to be selected must meet very specific criteria of acceptability to be considered eligible. The aim is to reduce risks, mitigate adverse events, and also to optimize the risk–benefit assessment according to the intended use of the high-risk device in question. Unfortunately, women, children, ethnic minorities, and aging populations are too often under-represented in clinical trials, thus introducing uncertainties about safety and effectiveness in these populations, which may compromise generalizability once the device is approved and introduced as standard clinical practice.[78]

2. Australia

Australia is also moving rapidly to improve its regulatory process due to recognized problems with the existing system. Between 2000 and 2011,

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[77] See e.g. Scott Brian Saxman, "Ethical Considerations for Outcome-Adaptive Trial Designs: A Clinical Researcher's Perspective" (2015) 29:2 Bioethics 59.

[78] See Daniel B Kramer et al, "Premarket Clinical Evaluation of Novel Cardiovascular Devices: Quality Analysis of Premarket Studies Submitted to the Food and Drug Administration 2000–2007" (2010) 17:1 Am J Ther 2 at 4; Brian L Egleston, Roland L Dunbrack, Jr & Michael J Hall, "Clinical Trials that Explicitly Exclude Gay and Lesbian Patients", Letter to the Editor, (2010) 36:11 New Eng J Med 1054; Mita Giacomini & Françoise Baylis, "Excluding Women from Medical Research: Reasons and Rejoinders" (2003) 3:10 Clinical Researcher 12, online: Yumpu.com <www.yumpu.com/en/document/view/33024653/view-article-novel-tech-ethics>; Sanket S Dhruva, Lisa A Bero & Rita Redberg, "Gender Bias in Studies for Food and Drug Administration Premarket Approval of Cardiovascular Devices" (2011) 4:2 Circ Cardiovasc Qual Outcomes 165; Medhna Ranganathan & Raj Bhopal, "Exclusion and Inclusion of Nonwhite Ethnic Minority Groups in 72 North American and European Cardiovascular Cohort Studies", online: (2006) 3:3 PLoS Med 0329 <www.plosmedicine.org/article/fetchObject.action?uri=info:doi/10.1371/journal.pmed.0030044&representation=PDF>; Maria CS Inacio et al, "Sex and Risk of Hip Implant Failure: Assessing Total Hip Arthroplasty Outcomes in the United States" (2013) 173:6 JAMA Intern Med 435; Anita Holdcroft, "Gender Bias in Research: How Does It Affect Evidence Based Medicine", Editorial, (2007) 100:1 J R Soc Med 2.

6,812 incidents involving MDs were reported to the Australian Therapeutic Goods Administration (TGA), including 295 deaths and 2,357 serious injuries.[79] Although McGee and colleagues' study does not describe which types of device were most often involved, these findings can lead one to conclude that there are important flaws in Australian premarket approval practices, particularly with regard to the way evidence is reviewed to ensure MD safety, quality, and efficacy. The TGA recently announced its intention to develop a series of reforms for MD regulation with the aim of increasing premarket assessment requirements concerning high-risk and especially implantable devices.[80] The TGA has also proposed reclassifying some types of MDs from medium- to high-risk (e.g., hip, knee, and shoulder joint replacement implants).

3. Japan

In Japan, before the introduction of new legislation in 2014, the last modifications to regulatory requirements for drugs and devices date back to 2005, one year after the 2002 amendments to the *Pharmaceutical Affairs Law* (*PAL*)[81] brought into creation the Pharmaceuticals and Medical Devices Agency (PMDA), the purpose of which was to harmonize Japan's requirements with international standard practices.[82] In 2011, the Japan Federation of Medical Devices Associations asked for more specific regulations to take into account the characteristics of MDs. In November 2013, the Japanese Parliament (the Diet) passed legislation revising the *PAL* – called the *Law for Partial Amendment of Pharmaceutical and Medical Device Law (Law no. 84)* – to officially separate marketing authorization holders for pharmaceuticals and devices, and also to put a greater focus on safety and qual-

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79 Richard G McGee et al, "Medical Device Regulation in Australia: Safe and Effective?" (2012) 196:4 Med J Aust 256 at 257.

80 Australia, Department of Health, Therapeutic Goods Administration, "Changes to Premarket Assessment Requirements for Medical Devices: Regulation Impact Statement" (26 June 2013), online: <www.tga.gov.au/regulation-impact-statement-changes-premarket-assessment-requirements-medical-devices>.

81 *Yakujihō* [*Pharmaceutical Affairs Law*], Law No. 96 of 31 July 2002.

82 See Y Furukawa, "Presentation on the New Japanese Pharmaceutical Affairs Law: Overview", PowerPoint presentation on behalf of Omnex Management and Engineering Consultants, LLC (January 2005) at 2, online: <www.omnex.com/training/iso13485/japan/Japan_regulatory_reqs-Jan_05.pdf>.

ity management systems, including greater involvement by the country's Ninsho review system with regard to some classes of MDs.[83] Interestingly, this new law introduces a definition of medical products that contain stem cells, which would thus be defined as regenerative and cellular medicine products.[84] It is also worth mentioning that, in 2014, the Japanese *PAL* was renamed *Act on Securing Quality, Efficacy and Safety of Pharmaceuticals, Medical Devices, Regenerative and Cellular Therapy Products, Gene Therapy Products, and Cosmetics*.

4. Canada

While the US, the EU, Australia, and Japan were working on tightening their controls over approval and diffusion of high-risk devices during the past three to four years, it was not clear that the existing regulatory framework in Canada would be revisited and assessed in light of new, emerging, and often complex technologies.[85] Striking examples of innovative but potentially problematic high-risk technologies include those at the brain–computer interface (e.g., a wireless, implantable neural prosthesis to translate neural signals from the brain),[86] active systems for improving the memory of Alzheimer's patients,[87] and implantable microchips such as radio-frequency

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83 For an English description of the law, see Japan, Ministry of Health, Labour and Welfare, *Outline of the Law for Partial Revision of the Pharmaceutical Affairs Law (Act No. 84 of 2013)*, online: <www.mhlw.go.jp/english/policy/health-medical/pharmaceuticals/dl/150407-01.pdf>.

84 Naoki Watanabe & Ayuko Nemoto, "Japan Enacts Regenerative Medicine Law and Revisions to Pharmaceutical Affairs Law" (18 December 2013), *K&L Gates LLP*, online: <www.klgates.com/japan-enacts-regenerative-medicine-law-and-revisions-to-pharmaceutical-affairs-law-12-17-2013/>.

85 Bruce Pastner, "FDA's Handling of High-Risk Medical Devices under the Microscope", Health Law Perspectives Working Paper [unnumbered] (2009), online: University of Houston Health Law & Policy Institute <www.law.uh.edu/healthlaw/perspectives/2009/%28BP%29%20Medical%20Devices.pdf>; Sheri Alpert, "Canadian Medical Device Regulations: Ready for Prime Time?" (2007) 6:2 CJLT 109 at 116.

86 Y-K Song et al, "Active Microelectronic Neurosensor Arrays for Implantable Brain Communication Interfaces" (2009) 17:4 IEEE Trans Neural Syst Rehabil Eng 339.

87 "Systems and methods for improving memory in Alzheimer's patients", US Patent No 8577470 (5 November 2013).

identification (RFID) that could be used for tracking people[88] or unlocking the door to one's car.[89] Other than developing an electronic submission pilot program for medium- and high-risk device licence and licence amendment applications in 2011, it seems that since 1998, Health Canada has not considered revisiting premarket or post-market review practices for MDs, especially to answer questions posed by the Auditor General of Canada about, for example, how often manufacturer establishments should be inspected; as a result, Health Canada did not know whether it was doing too many or too few inspections in a given year.[90] Post-approval/post-market inspections should normally be conducted during the first year following approval, with the goal of ensuring manufacturer compliance with regulations regarding manufacturing practices and labelling requirements. But as we will explain below, in 2014 the federal government decided to sponsor amendments to the *Food and Drugs Act*, through the *Protecting Canadians from Unsafe Drugs Act (Vanessa's Law)*,[91] an innovative strategy related to enforcing adverse-event reporting and post-market follow-up practices. Upon Royal Assent in November 2014, many of the key provisions of *Vanessa's Law* came into force.[92] In July 2015, final guidance was issued by Health Canada setting out a set of principles, policies, and standards to follow in situations where it may be appropriate for Health Canada to require a person to provide information, to disclose confidential information in certain circumstances, to order a label change or package modification, or to order a recall.[93]

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88 Paweł Rotter, Barbara Daskala & Ramón Compañó, "RFID Implants: Opportunities and Challenges for Identifying People" (2008) 27:2 IEEE Technology & Society Magazine 24.

89 Amal Graafstra, "Hands On: How Radio-Frequency Identification and I Got Personal" (28 February 2007), *IEEE Spectrum* (blog), online: <spectrum.ieee.org/computing/hardware/hands-on>.

90 Auditor General of Canada, *supra* note 15 at 13.

91 See Bill C-17, *supra* note 28.

92 SC 2013, c 24, amending *Food and Drugs Act*, RSC 1985, c F-27.

93 Health Canada, "Amendments to the *Food and Drugs Act*: Guide to New Authorities (Power to Require and Disclose Information, Power to Order a Label Change and Power to Order a Recall)" (last updated 31 July 2015), online: <www.hc-sc.gc.ca/dhp-mps/legislation/unsafedrugs-droguesdangereuses-amendments-modifications-eng.php>.

IV. Premarket Effectiveness Assessment

Even the most robust regulatory process and risk-classification system will be incomplete if it relies solely on premarket review, because this process cannot identify or predict all potential adverse outcomes, such as unanticipated reactions to biomaterials or drugs or unexpected device performance issues.[94] Medical devices are engineered to perform certain functions, according to specific performance and safety requirements, in order to provide the desired therapeutic effects for a specific intended use. But unlike the control point for approving drugs based on four phases of clinical trials – i.e., phases I to III (premarket) and phase IV (post-market), which alone often involves thousands of research participants – many MDs may not be subject to clinical trials, nor tested on large patient populations. As already mentioned, MD manufacturers have to demonstrate that the risks associated with the use of their device have been investigated and found acceptable when weighed against the benefits for the intended patient population, that their study meets international quality standards for the clinical investigation of MDs for human participants,[95] and that they have complied with all appropriate requirements when conducting clinical investigations to assess the safety or performance of the MD for regulatory purposes.[96]

Randomized controlled trials (RCTs) remain the gold standard for regulators and are the norm for pharmaceutical drugs. But for many MDs, this approach has serious limitations. RCTs may be inappropriate when the device addresses a small patient population or when the assessment of performance requires long-term follow-up (as is the case, for example, for orthopaedic implants). Just as for drugs, when a target patient population is relatively small and vulnerable, there may be no appropriate standard treatment for use as a control, something that often arises when the device or drug under investigation is a treatment of last resort. Furthermore, in the case of im-

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94 See Sunil V Rao et al, "Postmarket Evaluation of Breakthrough Technologies" (2008) 156:2 Am Heart J 201 at 204.

95 See International Organization for Standardization (ISO), "ISO 14155:2011 Clinical Investigation of Medical Devices for Human Subjects – Good Clinical Practice", online: <www.iso.org/iso/home/store/catalogue_tc/catalogue_detail.htm?csnumber=45557>.

96 See Maria Donawa, "US and European Postmarket Clinical Data Requirements" (2005) 16:2 Med Device Technol 36, online: Donawa Lifescience Consulting <www.donawa.com/medical-device/donawa/files/2%20Postmarket%20Clinical%20Data%20Mar2005%20MDT%20issue.pdf>.

plantable devices, using a placebo arm in a clinical trial would necessitate the use of sham surgery, which poses major ethical issues.[97] The choice of comparator or control arm raises significant ethical and practical considerations: how could one justify implanting a placebo vagus nerve system, for example? What other medical treatment or technology could be compared with a cochlear implant or DBS? Further, the clinical success (and thus the validity of the assessment) of implantable MDs such as hip or knee replacement prostheses, pacemakers, and even DBS systems may have a great deal to do with the skills of the surgeon involved and the patient selection criteria. Thus, findings from clinical trials may not be accurately indicative of the balance of harm and benefit for the broader patient population that will encounter these devices in standard clinical practice.[98]

There may also be situations in which trial findings introduce bias into the assessment process due to problems with recruitment. For example, patients who are the "best candidates" (i.e., most likely to respond positively) or individuals from relatively homogeneous study populations may be preferentially recruited into active or control groups, thereby favouring findings of positive device performance.[99] Conversely, an inability to recruit participants from certain groups (e.g., women or persons aged 65 years and older) may produce inaccurate safety and effectiveness findings when the results of studies are generalized across a treatment group. For instance, a study by Inacio and colleagues found dramatic safety concerns for women who received hip implants, with risks of failure 29% higher for women than for men, because men were overrepresented in the premarket clinical studies. This disparity in failure rate may be due to the fact that women generally have smaller joints and bones than men.[100] This situation could introduce

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97 See Heng Li & Lilly Q Yue, "Statistical and Regulatory Issues in Nonrandomized Medical Device Clinical Studies" (2008) 18:3 J Biopharm Stat 20 at 20; Wendy Rogers et al "Strengthening the Ethical Assessment of Placebo-Controlled Surgical Trials: Three Proposals", online: (2014) 15 BMC Med Ethics 78 at 2 <www.biomedcentral.com/content/pdf/1472-6939-15-78.pdf>; Alex J London & Joseph B Kadane, "Placebos that Harm: Sham Surgery Controls in Clinical Trials" (2002) 11 Stat Methods in Med Res 413 at 416.

98 Lawrence M Friedman, Curt D Furberg & David L DeMets, *Fundamentals of Clinical Trials*, 4th ed (New York: Springer, 2010) at 8.

99 Dhruva, Bero & Redberg, "Strength of Study Evidence", *supra* note 39 at 2683; Blake, *supra* note 42 at 120.

100 Inacio et al, *supra* note 78 at 440.

gaps in the data because of very low enrolment of some patient populations in early pivotal studies.[101]

Regardless of the particular design of a trial, a clinician-researcher has a legal and ethical obligation to explain to patients all the relevant medical information concerning the risks and benefits of a procedure so that the patient, as potential research participant, can decide whether or not to consent to the experimental procedure and take part in the study. Ensuring free and informed consent is fundamental to respecting the autonomy and self-determination of patients and research participants.[102] But informed consent can prove problematic because those people who need to use or to have implanted a high-risk device are most often accessing these technologies as last-resort procedures following the failure of other treatments or medications. While these patients may be severely ill or even incapacitated, with many experiencing a very poor quality of life, they may still be capable of understanding that they are undergoing surgery and participating in a research trial.[103] Their vulnerability does not mean that they are incapable of making an informed decision. Nonetheless, this vulnerability could affect their judgment and understanding of the actual and potential risks of a procedure, and they may also overestimate the anticipated benefits. Because these patients are seeking to improve their quality of life and capacities, to improve their family and social life, or even to get back to work, they may misunderstand the impact of the post-surgical long-term monitoring that is required with experimental devices, as well as the possible complications or discomfort of implanted MDs such as DBS or cardiovascular devices.[104]

In practice, many device trials – even those for high-risk devices such as cardiac pacemakers, stents, or DBS – move almost directly from feasibility studies to pivotal research, sometimes because randomization is considered

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101 Sanket S Dhruva & Rita F Redberg, "FDA Regulation of Cardiovascular Devices and Opportunities for Improvement" (2013) 36:2 J Interv Card Electrophysiol 99 at 103; Siobhán Cusack & Paul O'Toole, "Challenges and Implications for Biomedical Research and Intervention Studies in Older Populations: Insights from the ELDERMET Study" (2013) 59:2 Gerontology 114.

102 Bruce, *supra* note 68 at 104. See also Rogers et al, *supra* note 97.

103 See Ryan A Grant et al, "Ethical Considerations of Deep Brain Stimulation for Psychiatric Illness" (2014) 21:1 J Clin Neurosci 1 at 2; Emily Bell, Ghislaine Mathieu & Eric Racine, "Preparing the Ethical Future of Deep Brain Stimulation" (2009) 72:6 Surg Neurol 577 at 580; Rogers et al, *supra* note 97 at 5.

104 See Grant et al, *supra* note 103; Bruce, *supra* note 68 at 105.

unethical (e.g., the use of placebos or sham surgery), or because evidence can come from sources other than well-controlled clinical studies. The approval of MDs is thus often based on evidence from short-term, non-blinded or non-randomized studies involving small cohorts of patients that are rarely large enough to detect low-incidence effects.[105] Often, rare adverse events can be observed only after long-term, real-world use of a MD. For example, there was little data regarding the long-term overall risks and benefits of drug-eluting stents until the device had been approved in clinical practice, especially for higher-risk populations. The pivotal clinical trials were not prospectively designed to detect long-term or less frequent adverse effects, so it was only many years after approval that appropriate actions were taken to identify and respond to these adverse events.[106] Findings from a study that examined the evidence used by France's Haute Autorité de santé for implantable MDs prior to marketing showed that the level of evidence was in fact low and often based on insufficiently robust studies.[107] As such, it is often not possible to identify from premarket clinical studies all performance defects or low-frequency failures,[108] nor to obtain accurate evidence concerning the safety and effectiveness of long-term use of a device.[109]

V. Accessing Findings for All Trials

The difficulty in accessing all findings produced by clinical trials, at both the premarket and post-market levels, poses important challenges for ensuring the clinical obligation of beneficence/non-maleficence. As much for devices as for drugs, the fact that many industry-funded clinical trials

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105 Jeanne J Lenzer & Shannon Brownlee, "Why the FDA Can't Protect the Public" (2010) 341 Brit Med J c4753.

106 David F Kong, Eric L Eisenstein & Robert A Harrington, "Late Adverse Events after Drug-Eluting Stent Implantation" (2008) 10:4 Curr Cardiol Rep 253.

107 Laure Huot et al, "Medical Device Assessment: Scientific Evidence Examined by the French National Agency for Health – a Descriptive Study", online: (2012) 12 BMC Public Health 585 at 6 <www.biomedcentral.com/content/pdf/1471-2458-12-585.pdf>.

108 Robert G Hauser, "Here We Go Again: Another Failure of Postmarketing Device Surveillance" (2012) 366:10 New Eng J Med 873 at 874; Blake, *supra* note 42 at 119.

109 Jacqui Wise, "Medical Devices Regulation Needs to Be Overhauled, Says Cardiologist" (2011) 343 Brit Med J d6671.

still go unpublished can introduce significant biases that influence the strength of the research findings, thereby affecting the conclusions that can be drawn from them for clinical practice and public policy. This can pose a threat to human health and even hamper scientific progress,[110] because physicians as well as patients are then denied access to the full body of current scientific evidence, which is of utmost importance for informed consent and good clinical judgment.[111] Failing to publish clinical findings compromises the ability of clinicians, patients, and policy makers to make informed decisions about health care,[112] and it may constitute a breach of the obligation to inform people who have agreed to participate in a trial and who expose themselves to the risks of experimental interventions.[113] Some scholars have even gone so far as to argue that the under-reporting of research findings is in itself unethical and should be regarded as a form of scientific misconduct.[114]

Current regulatory requirements do not, however, ensure public access to all data coming from studies performed by manufacturers, even when posted to public registries such as ClinicalTrials.gov, a site maintained by the US National Institutes of Health. Findings from a study that examined 137,612 records from this database against 19,158 PubMed records showed that fewer than 15% of the completed studies registered on ClinicalTrials.gov had published results.[115] Further, Gordon and colleagues

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110 Daniele Fanelli & John PA Ioannidis, "US Studies May Overestimate Effect Sizes in Softer Research" (2013) 110:37 Proc Natl Acad Sci USA 15031 at 15031.

111 See Susan Portalupi et al, "Protocol for a Systematic Review on the Extent of Non-Publication of Research Studies and Associated Study Characteristics", online: (2013) 2 Syst Rev 2 at 2 <www.systematicreviewsjournal.com/content/pdf/2046-4053-2-2.pdf>.

112 RMD Smyth et al, "Frequency and Reasons for Outcome Reporting Bias in Clinical Trials: Interviews with Trialists" (2010) 342 Brit Med J c7153.

113 Nicholas J Gross, "Can You Believe It? Evidence of Publication Bias in Clinical Trial Reports", *Medscape* (15 September 2010), online: <www.medscape.com/viewarticle/728214> [subscription required]; Christopher W Jones et al, "Non-Publication of Large Randomized Clinical Trials: Cross Sectional Analysis" (2013) 347 Brit Med J f6104.

114 See e.g. Iain Chalmers, Paul Glasziou & Fiona Godlee, "All Trials Must Be Registered and the Results Published", Editorial, (2013) 346 Brit Med J f105.

115 Tatyana A Shamliyan & Robert L Kane, "Availability of Results from Clinical

showed that when trials were sponsored by government or non-profit organizations, results were more likely to be published within 24 months of study completion.[116] But it remains the case that studies with significant or positive results (as compared to negative results) are more likely to be published and to be accessible to the scientific and clinical communities, thereby creating a risk of positive bias.[117] The usefulness of the ClinicalTrials.gov database is further undermined when many registered trial findings remain unpublished,[118] which may be the case when trials are sponsored by industry, as companies have a vested interest in only publishing positive findings associated with their products.[119] Like the pharmaceutical industry, the MD industry may also be biasing clinical research through, for example, the choice of comparator agents and the publication of positive trial findings to the exclusion of negative results.[120]

In response to this systemic problem, the AllTrials Campaign (www.alltrials.net), launched in January 2013 as an initiative of the *Bad Science* blog, the *British Medical Journal*, Oxford University's Centre for Evidence-Based Medicine, the Cochrane Collaboration, the James Lind Initiative, PLOS, and the UK-based Sense About Science, is calling for the mandatory registration of all clinical trials performed throughout the US and in the EU

Research: Failing Policy Efforts" (2014) 4:1 J Epidemiol Glob Health 1 at 4.

116 Florence T Bourgeois, Srinivas Murthy & Kenneth D Mandl, "Outcome Reporting among Drug Trials Registered in ClinicalTrials.gov" (2010) 153:3 Ann Intern Med 158 at 164.

117 F Song et al, "Dissemination and Publication of Research Findings: An Updated Review of Related Bias" (2010) 14:8 Health Technol Assess 21 at 32; Sally Hopewell et al, "Publication Bias in Clinical Trials Due to Statistical Significance or Direction of Trial Results (Review)" [2009] 1 Cochrane Database Syst Rev.

118 A recent study published in the *New England Journal of Medicine* confirms that in over 13,000 trials registered on ClinicalTrials.gov, only 13.4% of those trials reported results within the first year. See Monique L Anderson et al, "Compliance with Results Reporting at ClinicalTrials.gov" (2015) 372:11 New Eng J Med 1031 at 1034.

119 Bourgeois, Murthy & Mandl, *supra* note 116 at 165; Jones et al, *supra* note 113 at 3.

120 Joel Lexchin, "Those Who Have the Gold Make the Evidence: How the Pharmaceutical Industry Biases the Outcomes of Clinical Trials of Medications" (2012) 18:2 Sci Eng Ethics 247 at 251–52.

member states, as well as for the public disclosure of full study findings to the medical community and to patients. Such a process could help ensure that clinicians and patients are not misled about the benefits and risks of a drug or device, enable regulatory bodies to detect potentially important problems with a new technology, contribute to research planning, and promote more rational use of drugs and MDs.[121] The purpose of this database is to make mandatory the registration of all trials carried out in the EU, with a summary of results to be submitted one year after the end of each registered trial. Under the proposal, clinical study reports should in general no longer be considered confidential commercial information, and fines would be imposed by member states for non-compliance with the transparency requirements. In December 2013, the EU's Committee of Permanent Representatives endorsed a provisional agreement aimed at the development of a public EU database to be set up and run by the EMA. And in April 2014, the European Parliament passed a law that will require all clinical trials to be registered and to report results in Europe starting in 2016.[122]

In Canada, *Vanessa's Law* constitutes a major step towards ensuring the transparency of data collected at premarket and post-market levels, given the amendments that are to be introduced into the *Food and Drugs Act* to make public all information about clinical trials.[123] Unfortunately, the law states that such publication requirements may be set at the discretion of the Minister of Health, thus making transparency measures conditional.[124] This would not guarantee that both positive and negative data would become available for independent and timely scrutiny.[125] In March 2015, Health Canada launched a large, 60-day consultation with different stakeholders

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121 Peter C Gøtzsche, "Deficiencies in Proposed New EU Regulation of Clinical Trials" (2012) 345 Brit Med J e8522.

122 EC, European Parliament, Committee on the Environment, Public Health and Food Safety, Press Release, "Clinical Trials: Clearer Rules, Better Protection for Patients" (2 April 2014), online: <www.europarl.europa.eu/pdfs/news/expert/infopress/20140331IPR41186/20140331IPR41186_en.pdf>.

123 Bill C-17, *supra* note 28, s 21.7.

124 *Ibid*, s 21.1

125 Matthew Herder, "The Opacity of Bill C-17's Transparency Amendments" (23 June 2014), *Impact Ethics* (blog), online: <impactethics.ca/2014/06/23/the-opacity-of-bill-c-17s-transparency-amendments/>; Mathew Herder et al, "Regulating Prescription Drugs for Patient Safety: Does Bill C-17 Go Far Enough?" (2014) 186:8 CMAJ E287 at E290–91.

to seek comments to determine what information should be made public and when. Unfortunately, the final report concerning the *consultation document* has not yet been publicly released. In June 2015, the Honourable Rona Ambrose, then Minister of Health, launched Health Canada's Regulatory Transparency and Openness Framework and Action Plan 2015–2018 to outline concrete steps and measures to improve open access to timely, useful, and relevant health and safety information related to medical and food products.[126]

VI. Post-market Regulatory Practices

Demonstration of device performance at the level of premarket assessment does not necessarily mean that there is proof of clinical safety and efficacy at the post-market level.[127] The result of such limited premarket clinical evidence is that once a MD is approved, there may still be substantial uncertainties regarding the safety and effectiveness of the device in clinical practice.[128] Clinicians employing such devices must then rely on their individual clinical experience and adverse-event notifications from regulatory authorities to judge which MD is appropriate for their patient. High-risk MDs, and more particularly implantable and surgically invasive MDs intended for long-term use, require more comprehensive and robust evidence at the premarket level. To enable this, manufacturers must be required to produce better and more accurate clinical data.

The evidence required for regulatory approval must show that a MD will perform as intended in a defined population when used for a very specific intervention. But, unlike drugs, and for the reasons discussed earlier, MDs are often much less likely to have demonstrated clinical safety prior to being marketed. We may think that once on the market, MDs would then be subject to various (and rigorous) forms of post-marketing surveillance practices, specifically with regard to adverse-event reporting, to ensure adequate performance in the clinical practice environment (see Table 2). Unfortunately, it seems that post-market surveillance mechanisms are deficient in capturing

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126 Health Canada, Regulatory Transparency and Openness Framework and Action Plan 2015–2018, online: <www.hc-sc.gc.ca/home-accueil/alt_formats/pdf/rto-tor/2015-18-fap-cpa-eng.pdf>.

127 Hulstaert et al, *supra* note 38.

128 Deborah Cohen & Matthew Billingsley, "Europeans Are Left to Their Own Devices" (2011) 342 Brit Med J d2748.

unexpected adverse outcomes and measuring performance outcomes.[129] In the EU, for instance, the clinical performance of high-risk MD is still not subject to any premarket authorization by a regulatory authority, as these devices only require a conformity assessment; that is, to enter the European market, they must simply comply with the relevant legislation, i.e., Directive 93/42/EEC (applicable to MDs) or Directive 90/385/EEC (applicable to active implantable devices).[130] The weaknesses with such a system were highlighted by an international scandal in 2012 involving the French company Poly Implant Prothèse (PIP), a manufacturer of silicone breast implants. For several years, PIP had used an industrial silicone gel commonly used as a mattress filler, instead of the medical grade silicone approved by EU regulators.[131] The result was that in spite of existing MD regulations and oversight, hundreds of thousands of women around the world were implanted with a dangerous device that then had to be removed. The time has come, we argue, to move towards more stringent regulatory requirements for risk and evidence assessment of high-risk MDs.

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129 Arjun Sharma et al, "Health Care Policy and Regulatory Implications on Medical Device Innovations: A Cardiac Rhythm Medical Device Industry Perspective" (2013) 36:2 J Interv Card Electrophysiol 107 at 110.

130 EC, *Council Directive of 20 June 1990 on the approximation of the laws of the Member States relating to active implantable medical devices (90/385/EEC)*, [1990] OJ, L 189/17; EC, *Council Directive 93/42/EEC of 14 June 1993 concerning medical devices*, [1993] OJ, L 169/1; both as amended by EC, *Directive 2007/47/EC of the European Parliament and of the Council of 5 September 2007 amending Council Directive 90/385/EEC on the approximation of the laws of the Member States relating to active implantable medical devices, Council Directive 93/42/EEC concerning medical devices and Directive 98/8/EC concerning the placing of biocidal products on the market*, [2007] OJ, L 247/21. See also Campillo-Artero, *supra* note 44 at 41.

131 Eleanor Beardsley, "Fears Grow over Faulty French-Made Breast Implants", *National Public Radio* (5 January 2012), online: <www.npr.org/2012/01/05/144748209/fears-grow-over-faulty-french-made-breast-implants>; Rebecca Smith, "Pips Breast Implant Scandal: Regulator Warned Years Earlier", *Telegraph* (15 May 2012), online: <www.telegraph.co.uk/health/healthnews/9264541/Pips-breast-implant-scandal-Regulator-warned-years-earlier.html>; Daniel Piotrowski, "Dramatic Rise in PIP Breast Implant Ruptures in Australia", *News.com.au* (11 October 2012), online: <www.news.com.au/lifestyle/health-fitness/bursting-staggering-amount-of-breast-implants-explode/story-fneuz9ev-1226492298726>.

Post-market surveillance mechanisms have thus become increasingly important. Regardless of the rigour of the premarket review process, it would be unrealistic to expect that all possible device failures or incidents arising from device use can be predicted. It is through real-world use that unforeseen problems related to safety and effectiveness can be detected.[132] It is important, then, that regulators monitor how a device actually performs once it is used in large patient populations, i.e., once it is approved for marketing. National regulatory authorities and manufacturers keep track of the manufacturing and the use of devices, for example, through inspections of manufacturing establishments, collecting and reporting device failures, and monitoring adverse-event reports communicated by manufacturers, health care professionals, health care facilities, and even patients. Regulatory authorities should also monitor and assess scientific and medical information about the consequences of incidents and potential risks a device may pose in order to issue warnings in a timely manner or remove a device from the market.[133]

Another challenge with regard to post-market practices concerns the reporting of incidents or adverse events associated with the use of MDs, especially high-risk MDs. Incident reporting is a major source of data for post-market risk assessment and is essential to understanding the long-term benefits and risks in real-world practice. In the case of high risk MDs – some of which are implanted for long-term use, if not permanently – problems with safety and effectiveness that are not captured at the premarket level due to short-term and small-cohort clinical studies may only appear after a substantial period of time, by which point the patients may be receiving devices that differ from those selected in the pre-approval studies.[134]

Yet, while it is compulsory for manufacturers to report any incident to national regulatory authorities, manufacturers have the freedom to decide when a negative outcome is unrelated to a device.[135] Further, reporting adverse outcomes remains voluntary for health care facilities, health care professionals, and patients, which should raise concerns about the accur-

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132 World Health Organization, *Medical Device Regulations*, *supra* note 32 at 13.

133 Auditor General of Canada, *supra* note 15 at 8; Elisabethann Wright & Steven Datlof, "Adverse Event Reporting in the EU and the USA: Similarities and Differences" (2010) 7:3 J Medical Device Regulation 14 at 18.

134 Dhruva & Redberg, *supra* note 101 at 100, 102.

135 *Ibid* at 102.

acy and completeness of adverse incidence data. For example, patients may not even know that they can report device problems to the manufacturer and/or government health authorities.[136] Reporting by health care providers is also significantly lacking. The Office of the Inspector General of the US Department of Health and Human Services (DHHS) reported that between 2003 and 2007, only 6% of adverse-event reports came from health care providers, users, and distributors.[137] This figure is similar to findings in other countries: 10% of adverse outcomes in Canada and 12% of adverse outcomes in Australia (in 2009) were submitted by health care providers or patients/users.[138] Moreover, there is no routine or systematic review of reported adverse events, so it may take time before regulatory agencies publicly disclose them; for example, Dhruva and Redberg report the case of the Bard inferior vena cava (IVC) filter, which accumulated 921 adverse-event reports before the FDA made them public.[139]

Nonetheless, as already mentioned, a significant increase in adverse-event reporting has been observed in recent years. In the US, adverse-event reports rose from 57,000 in 2001 to more than 207,000 in 2009; in 2003, 27% of adverse-event reports were associated with Class III devices, but by 2009 this figure had grown to 40%.[140] In Australia, 47.5% of the 6,812 incidents involving MDs that were reported between 2000 and 2009 were not investigated.[141] Health Canada does not perform any better, according to a 2011 report from the Auditor General of Canada, because it fails to assess whether incident reports on specific devices have been reviewed according to the risks identified or whether the reports are reviewed in a timely man-

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136 Blake, *supra* note 42 at 122.

137 US, Department of Health and Human Services, Office of Inspector General, *Adverse Event Reporting for Medical Devices* (October 2009) at 9, online: <oig.hhs.gov/oei/reports/oei-01-08-00110.pdf>.

138 Health Canada, *Underutilization of the Adverse Reaction Reporting System* (20 June 2007), online: <epe.lac-bac.gc.ca/100/200/301/pwgsc-tpsgc/por-ef/health/2007/385-06/report.pdf>; McGee et al, *supra* note 79 at 258.

139 Dhruva & Redberg, *supra* note 101 at 101.

140 US, Food and Drug Administration, *Understanding Barriers to Medical Device Quality* (31 October 2011), online: <www.fda.gov/downloads/AboutFDA/CentersOffices/CDRH/CDRHReports/UCM277323.pdf>.

141 McGee et al, *supra* note 79 at 259.

ner.[142] Under-reporting as much as under-assessment of adverse events has important consequences for the patients affected by these device failures, for their clinicians who must find alternative therapies, and for regulators who may lack up-to-date data to identify the causal factors and thereby determine an appropriate response.[143] Finally, the early detection of device failures or negative outcomes may save hundreds if not thousands of patients from being exposed to unnecessary risks and painful complications.

Adverse-event reporting does not, however, always allow for a quantification or understanding of the nature of the risks involved with a particular MD. The ability to make causal associations between the use of a specific technology or drug and the frequency of known or new reactions may be extremely difficult.[144] Post-market studies may thus be a particularly important tool for post-market surveillance practices because they can assess device performance and safety, detect problems, and monitor conditions of use once a device enters the market. For example, patient-reported outcome studies may provide information about patient perspectives and experiences.[145] Information about performance of approved devices generated from post-market study data could be an important means of identifying trends and use in clinical settings, and could thus provide a better understanding of appropriate follow-up that may be needed in certain circumstances,[146] such as when the findings were not sufficiently supported by premarket clinical data[147] or because patients enrolled in post-market studies may have

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142 Auditor General of Canada, *supra* note 15 at 27.

143 See e.g. McGee et al, *supra* note 79; Aleksandar Videnovic & Leo Verhagen Metman, "Deep Brain Stimulation for Parkinson's Disease: Prevalence of Adverse Events and Need for Standardized Reporting" (2008) 23:3 Mov Disord 343.

144 Kerri Mackay, "Showing the Blue Card: Reporting Adverse Reactions" (2005) 28:6 Aust Prescr 140; JR Nebeker, P Barach & MH Samore, "Clarifying Adverse Drug Events: A Clinician's Guide to Terminology, Documentation, and Reporting" (2004) 140:10 Ann Intern Med 795; Lian Duan et al, "Adverse Drug Effection Detection" (2013) 17:2 IEEE J Biomed Health Inform 305.

145 RC Macefield, KNL Avery & JM Blazeby, "Integration of Clinical and Patient-Reported Outcomes in Surgical Oncology" (2013) 100:1 Br J Surg 28 at 28.

146 See e.g. Robert W Yeh et al, "Do Postmarketing Surveillance Studies Represent Real-World Populations? A Comparison of Patient Characteristics and Outcomes after Carotid Artery Stenting" (2011) 123:13 Circulation 1384.

147 Stephen Rothenberg & Matt Levy, "Proactive Postmarket Safety Surveillance

different characteristics and outcomes from those who participated in the pre-approval clinical trials.[148] Longer clinical experience may help identify unforeseen concerns or low-frequency failures or outcomes[149] and identify new safety concerns.[150] Finally, findings from post-market studies may become useful for HTA agencies when they have to review new or on-the-market devices and issue recommendations about their coverage (i.e., use and reimbursement) within the health care system.

VII. RECOMMENDATIONS

A. Premarket

Although the many regulatory changes announced in recent years by the EU, Australia, and the US provide hope that there will be important improvements in premarket review, the current differences between jurisdictions remain substantial. Harmonizing national classification systems could offer significant benefits to manufacturers, users, patients, and regulatory authorities, and even support global convergence of regulatory systems.[151] Many high-risk devices are designed to assist very sick patients suffering from medical conditions or disabilities which cannot or can no longer be treated through drugs; currently, thousands of patients rely on lifesaving

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in Scrutinized World" (22 February 2012), *Medical Device and Diagnostic Industry*, online: <www.mddionline.com/article/risk-management-postmarket-surveillance>.

148 Dhruva & Redberg, *supra* note 101 at 102.

149 Daniel B Kramer et al, "Postmarket Surveillance of Medical Devices: A Comparison of Strategies in the US, EU, Japan, and China", online: (2013) 10:9 PLoS Med at 5 <www.plosmedicine.org/article/fetchObject.action?uri=info:doi/10.1371/journal.pmed.1001519&representation=PDF>; Hauser, *supra* note 103 at 874.

150 Joseph S Ross et al, "Post-Market Clinical Research Conducted by Medical Device Manufacturers: A Cross-Sectional Survey" (2015) 8 Med Devices (Auckl) 241 at 245.

151 Global Harmonization Task Force, *Principles of Medical Devices Classification* (final document, 2 November 2012), online: International Medical Device Regulators Forum <www.imdrf.org/docs/ghtf/final/sg1/technical-docs/ghtf-sg1-n77-2012-principles-medical-devices-classification-121102.docx>.

MDs.[152] Faced with a proliferation of MDs internationally and the rapid pace of innovation in the field, ensuring device safety and performance is of utmost importance for patients. For example, many new emerging technologies will incorporate nanomaterials, medicinal products, or biological materials or may be connected to an energy source; these developments necessitate timely public access to the best evidence drawn from findings from all clinical studies conducted around the world. Failure to submit negative data is in itself a major ethical issue. Not only can it create bias, but when regulatory authorities, decision makers, and users have to rely on incomplete evidence, they may overestimate the safety and performance of a MD.[153] As much as regulatory authorities should not be denied access to unpublished findings, high-risk MDs should not be cleared for use without clinical testing, even when long-term trials may not always be possible.[154] Regulatory agencies have a dual mandate of ensuring patient safety and providing timely access to new medical treatments.[155]

We thus support Kaplan and Williams,[156] who suggest a two-step approval process: an *initial* approval and a subsequent *final* approval once a device has entered into clinical use, contingent on accumulated clinical experience at specific end-points. Admittedly, granting only conditional approval for a specified period may impose a financial burden on manufacturers, and health care providers or health care facilities may have reservations about offering their patients a conditionally approved device. Further, both public and private health care payers may refuse to cover the costs of such MDs because of insufficient evidence of effectiveness or lack of substantial evidence of safety, and regulatory agencies may be reluctant to issue final approval even when no alternative exists, so as to protect vulnerable

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152 Hauser, *supra* note 108 at 874.

153 Kay Dickersin & Iain Chalmers, "Recognizing, Investigating and Dealing with Incomplete and Biased Reporting of Clinical Research: From Francis Bacon to the WHO" (2011) 104:12 J R Soc Med 532 at 532.

154 Wise, *supra* note 109.

155 Nicholas S Downing et al, "Regulatory Review of Novel Therapeutics – Comparison of Three Regulatory Agencies" (2012) 366:24 New Eng J Med 2284 at 2291.

156 Aaron V Kaplan & David O Williams, "Medical Device Regulatory Landscape: The Imperative of Finding Balance" (2012) 5:1 Circ Cardiovas Interv 2 at 4.

patients.[157] Yet this approach could allow earlier access to new medical technologies if there are no safety issues already known prior to their marketing. Nonetheless, this approach calls for negotiation between all concerned stakeholders, including those with HTA expertise, to develop explicit criteria for accumulating the necessary scientific evidence and conditions to inform decisions about access and coverage by health care systems.

B. Post-market surveillance

In 2011, following a recommendation of the US Government Accountability Office, Senators Grassley, Blumenthal, and Kohl (unsuccessfully) introduced the *Medical Device Patient Safety Act* in the House of Representatives, which would have required a conditional approval approach to MD regulation in order to protect patients from unsafe medical devices, especially those cleared through the 510(k) approval pathway. This new process sought to improve post-market practices by empowering the FDA to impose conditions on the sale and distribution of a device (namely data collection, labelling information, and post-market studies) while it is undergoing further evaluation for potential testing of its safety, effectiveness, and reliability.[158]

We argue for some form of *conditional* approval based on more data obtained through post-market studies in the case of high-risk MDs, and especially for active implantable devices. As much as for pharmaceutical drugs, post-market studies of MDs can provide all concerned stakeholders (regulators, health care providers, patients, and HTA agencies) with useful risk–benefit performance evidence concerning new products in real-world clinical practice.[159] User-friendly mechanisms need to be implemented to facilitate more frequent and even mandatory reporting of adverse events by users who are directly involved, i.e., patients and health care providers.

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157 Darroy et al, "Practical, Legal, and Ethical Issues in Expanded Access to Investigational Drugs" (2015) 372:3 New Eng J Med 279.

158 US, Bill S 1995, *Medical Device Patient Safety Act*, 112th Cong, 2011; see also "Medical Device Patient Safety Act" (bill summary), *Hyman, Phelps & McNamara, PC*, online: <www.hpm.com/pdf/blog/Medical%20Device%20Patient%20Safety%20Act%20Summary%20PDF.pdf>.

159 Hans-Georg Eichler et al, "Balancing Early Market Access to New Drugs with the Need for Benefit/Risk Data: A Mounting Dilemma" (2008) 7:10 Nat Rev Drug Discov 818 at 824.

When gaining access to a high-risk device, patients should receive all appropriate and convincing evidence about the nature of the device, details regarding its manufacturing company, and information about its potential outcomes, and they should be invited to report any adverse outcomes not only to their physicians but also to the appropriate regulatory authorities. For now, most patients are still confident that their physicians or hospital facilities will take charge of such reporting, a confidence that is likely misplaced. Proactive post-market surveillance practices should not be limited to corrective or preventive actions, such as inspections and adverse events reporting; they should instead serve to review the effectiveness and performance of a device in routine clinical practice, in order to provide objective information for decision making in health care delivery and health policy.[160]

Reliable clinical registries should also be encouraged. Australia recently evaluated the benefits of developing national quality registries for high-risk implantable devices to provide clinical data from identified individuals who have received those devices and to facilitate disclosure of potential and unforeseen problems with any specific type of device.[161] With the increasing complexity of high-risk devices, such registries may facilitate access to real-world use of data on performance, safety, clinical effectiveness, and reliability and provide critical information on the frequency of device malfunctions or complications.[162] All national jurisdictions should align their practices to those of the FDA, which is promoting the development of national device registries that are independent of manufacturers' registries and the sharing of information with other national registries (where they exist) to generate new data.[163]

More importantly, device traceability practices should become a key post-market surveillance practice to improve safety and performance capabilities. In July 2012, the FDA proposed a rule for establishing a unique

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160 Markus Siebert et al, "Health Technology Assessment for Medical Devices in Europe" (2002) 18:3 Int J Technol Assess Health Care 733 at 736.

161 Australia, Department of Health and Ageing, *Regulation Impact Statement: Clinical Registers for High Risk Implantable Medical Devices* (18 February 2013), online: Australia, Department of the Prime Minister and Cabinet, Office of Best Practice Regulation <ris.dpmc.gov.au/files/2013/06/RIS_Clinical_Registers.pdf>.

162 Sharon-Lise T Normand et al, "Postmarket Surveillance for Medical Devices: America's New Strategy" (2012) 345 Brit Med J e6848.

163 *Ibid* at 1.

device identification (UDI) system in order to improve patient safety and make post-market follow-up more efficient throughout the whole life cycle of a device. This measure could help identify product problems more quickly and enable better and more targeted recalls, thereby enhancing patient safety. A UDI could take the form of a unique permanent marking (e.g., a unique numeric or alphanumeric code) specific to any device, and would allow more accurate reporting, reviewing, and analyzing of adverse-event reports. This would then allow problem devices to be identified and corrected more quickly, improve incident reporting, reduce medical errors, and even help fight the use of counterfeit devices.[164] All UDIs should be designed to be readable by humans and machines and should be used in the supply chain software of health systems, in electronic health records, and in registries; needless to say, such a system could greatly facilitate device tracking, safety surveillance, and research.[165]

Conclusion

Innovations in the field of MDs aim at improving patient care and responding to unmet health care needs. Yet high-risk MDs pose particular ethical and policy challenges that can undermine the responsibilities of clinicians and regulators to work in the best interests of patients, ensure public safety, and protect public health. Current regulatory practices contribute to an ongoing lack of high quality evidence associated with premarket clinical studies, the non-public disclosure of new evidence, and inadequate data on the overall use and long-term outcomes of high-risk MDs.[166] The time has come to improve harmonization among national regulatory systems, especially for high-risk MDs, in both the premarket assessment of evidence (e.g., classification and premarket safety and performance requirements for clinical assessment) and in post-market surveillance. In the face of the rapid development of complex and sophisticated medical technologies, current regulatory processes appear inadequate to ensure not only patient safety but also informed decision making by patients, health care providers, and third-party payers. We argue that the device development process should be seen as a continuum, beginning with first clinical use and extending initially to

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164 *Cf* FDA, *Final UDI Rule*, *supra* note 57 at 58786.

165 Normand et al, *supra* note 162 at 1.

166 Hulstaert et al, *supra* note 38; Normand et al, *supra* note 162.

market launch and then to eventual use in routine clinical practice.[167] Regulation may be an imperfect tool, but it is nonetheless essential to ensuring that patients receive the right treatment for the right condition and benefit from safe and effective MDs. It is a matter of both personal and public health.

The creation of the Globalization Harmonization Task Force was a Canadian initiative, so it is disappointing to see that Canada is lagging behind the other founding member nations in updating its regulatory system. Given the many measures adopted by the US, Australia, Japan, and the EU with regard to high-risk MDs, it is time that Canada moves forward on adapting its current system and working with its partners in the new International Medical Device Regulators Forum[168] to harmonize practices across national jurisdictions. Such a development would help eliminate differences between jurisdictions, decrease the costs of regulatory compliance, and address major ethical and policy concerns associated with the accurate risk–benefit assessment of high-risk MDs, both before and after they enter the marketplace and become part of clinical practice and health service provision.

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[167] Roxana Mehran, "Post-Market Approval Surveillance: A Call for a More Integrated and Comprehensive Approach" (2004) 109:25 Circulation 3073 at 3077.

[168] See *supra* note 9 and accompanying text.

APPENDIX. SOURCES FOR TABLE 2

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