



**The Ethics of Innovation in the Medical Device Industry:
A Complex Interaction between Multiple Actors and a Search for a
Novel Approach**

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Abstract

Ethics are inexorably linked to innovation and the release of new technology in the medical device industry. This thesis explores the ethical responsibilities of the actors within the industry, and questions the effectiveness of Premarket Notification [510(k)] regulation to adequately and ethically regulate the release of medical devices. Revision or redefinition of 510(k) policy is strongly suggested to properly address concerns of safety and efficacy in the ethical release of innovation to the public.

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The stakes are high, from both the value of progress and the price paid by patients and society if the innovation fails (Malchau, Bragdon, and Muratoglu 825-31).

Introduction

Ethics are inexorably linked to innovation and regulation in the medical device industry. Undue burden on innovation can introduce stress to ethical boundaries. Corporate focus is tenuously perched between profit and patient safety. When one or the other is threatened, pressure increases and ethics are challenged. Likewise, each actor involved faces multifaceted pressures. Regulation has been put in place to provide an ethical platform for the creation and sale of medical devices, but the current regulatory framework in the United States does not adequately protect the public and needs reform. It should be the goal of each party to eliminate as much burden as possible to allow innovation to thrive in an ethical environment with the patient's best interests in mind. The ideal model would necessitate strict regulation and penalties for unethical behavior thus encouraging ethical behavior through the regulatory structure, but would allow avenues for innovation. Truly innovative products would still succeed, and only the imposters should be alarmed.

Thesis Scope

Regulatory policy in the United States is flawed. Distribution of innovative new technologies must be ethically controlled through redefinition of the Premarket Notification [510(k)]¹ process. This thesis explores the ethical responsibilities of the actors (manufacturer, regulator, provider, and consumer) within the industry, particularly their relationship to each other in the release

of new technology, and questions the effectiveness of 510(k) regulation to adequately and ethically regulate the release of medical devices.

Background

There is a constant development and release of new products within the medical device industry, and it is becoming increasingly important to weigh the ethical concerns tied to innovation and the release of new technology. Ethical dilemmas become increasingly complex because of all the actors involved. This thesis will explore:

- 1) the tension between the desire for newer and better performing technologies and the consequent desire to get these products to the consumer (while making a profit), and
- 2) the inherent risk associated with launching new technologies that have not yet shown the robust clinical success which is necessary for making adequate determinations of safety and efficacy, and allows a more accurate view of the risks compared with the benefits.

Ultimately, changes are necessary in the roles of each of the primary actors involved in the medical device clearance process to ensure innovation is pursued ethically in a fast changing environment.

The scope of this project will be limited to technological innovation in the medical device industry, to the exclusion of innovation of the processes for how consumers buy and use new products and the business models associated with delivering them, along with innovative surgical technique.

Medical device regulation in the United States is in place to ensure the products being marketed are safe and functioning as intended, but additionally, the goal is to allow innovative products that fit this standard to be available to the public as quickly as possible. The manufacturer, the provider, and the consumer have similar goals, but there seems to be friction between the parties.

The government (or regulator) is being pressured from both sides. They face pressure from the public over safety debacles fresh on our collective memory and pressure from the manufacturer and provider to speed up reviews and approvals for new devices and modifications to existing devices. The manufacturer feels pressure to innovate, but also bears an extreme burden – rightly so – to produce devices that are safe and work as they ought. Recent litigation being brought against various manufacturers through class-action lawsuits adds growing incentive to release products that are “successful.”²

The provider (hospitals and surgeons) face multi-faceted pressures as well. There is a continued pressure to reduce prices in healthcare to achieve profitability and alleviate the burden to the consumer, but there is also pressure to provide the “newest and best,” and to provide the newest or best usually means a device that is more expensive, and more importantly, a device that typically has little or no clinical history. Waiting for clinical data, however, necessarily threatens losing the distinction of “new.” It may seem difficult to understand why we are so quick to seek new designs for a device that has multiple iterations on the market that consistently last 15 to 20 years (hip and knee replacements), but if I were a 50-year-old patient

in need of a hip or knee replacement, I would certainly be willing to at least *consider* trying a device that might last the rest of my life, even if I lived into my nineties.

Regulations exist to protect the end-user of medical devices – the patient – but do the regulations work? Is there a better way to ethically pursue innovation in the medical device industry? Or asked differently, is there a better way to ethically release innovative products to the consumer? To successfully make headway in sparking a change in our current environment, the actors must be aligned. Each must take responsibility for their unique role in the process. I seek to illuminate the relationships between the actors in the medical device industry and help the reader better understand the unique ethical responsibilities in innovation that resonates with the part that we all have been given to play.

A brief description on innovation in this particular field would be beneficial before getting too much further. Innovation in the medical device industry typically occurs through small, painstaking changes to existing devices. Even devices touted as “new” or “unique” are usually just variations of a design already on the market. It can be legitimately argued, however, that even small changes can provide enormous benefits to patients. Contrarily, small changes have produced disastrous results (see the following metal-on-metal hip and bone cement case studies). Regulation in the United States does not exist to stifle innovation. In fact, it is much the opposite. Regulation *seeks* to insure it is the truly innovative products (the ones that work) that make it to the market, and at their core is a desire to provide innovative products to the consumer as quickly as possible. The government does not want to stand in the way of life-saving or life-altering products, but this “expedite” mentality can backfire, and it has the

potential to creep into the corporate thinking of all the actors involved. For instance, a manufacturer may simply take advantage of specific regulatory pathways available to them for getting a product to market, as opposed to weighing the ethical considerations of the offering and developing a proper plan for its distribution, even if that means going above and beyond the existing regulatory requirements. These dilemmas become increasingly complex as the many different global regulatory requirements are taken into consideration, but we will focus primarily on US regulation to keep the scope of the topic from becoming unwieldy. I argue that our current system contains flaws, particularly within the 510(k) regulation that ethically demand to be addressed.

At the heart of this dilemma is the following paradox: most of the time, when a minor modification is made to an existing device to create a “new” product, the design is claimed as substantially equivalent to a previously marketed device, or one currently on the market, when asking the FDA for a more limited approval process; however, as soon as the claim is granted by FDA, the device is touted for its uniqueness and all the significant ways that it is different from its predecessors are brought to the forefront. The process seems skewed in relation to the ethical responsibility to the consumer and the provider. What good is innovation if it does not benefit the consumer?

Historical Context

Before delving into the specifics of medical device regulation, ethics, and innovation and the release of new technology, it would help to detail some cases which highlight the flaws in the regulatory system and the ethical dilemmas that are faced when discussing the introduction of

new technology. The following case studies are just a few of the many examples of failed innovation in the field (Huiskes 699-716;Green 260-66) but serve to provide appropriate context for our discussion about how situations like these can occur within our current regulatory paradigm and what our ethical responsibilities are in attempting to eliminate future failures.

Metal-on-Metal Hip Case Study

In July of 2008 DePuy's ASR XL Acetabular Cup System (ASR XL) received clearance for sale and marketing in the United States by FDA. The ASR XL is a hip implant which replaces the hip joint's normal articulating surface with two metal surfaces – a metal acetabular cup and a metal stem and ball that articulates within the cup. The picture below shows a similar metal-on-metal hip implant device.



Figure 1: Birmingham Hip Resurfacing Device (Daniel, Pynsent, and McMinn 177-84)

In theory, the concept of a metal-on-metal articulation seemed promising in terms of wear and longevity. The metal used, cobalt chrome (CoCr) is very biocompatible and a material used for

many implantable devices. However, in other orthopaedic applications the metal components do not typically move (articulate) directly on each other. For example, in a knee implant, and in other hip implants, a plastic (polyethylene) insert is placed between both metal components so the articulation happens as metal-on-polyethylene.

In the United States, the ASR XL implant was cleared for sale through 510(k) regulation. No clinical performance data was required because the device was claimed as substantially equivalent to existing devices. Ardaugh et al. explain that the ASR XL implant was really a unique combination of three features: porous ingrowth material, metal-on-metal articulation, and larger than normal femoral head sizes. They also reveal that the submission claimed substantial equivalence to three devices that were on the market before 1976, and those devices had long since been discontinued because their risk of revision was higher than other devices (Ardaugh, Graves, and Redberg 97-100).

In the case of the ASR implant, it became apparent quickly that something was not right. Many patients started reporting groin pain and surgeons began seeing high rates of implant failure, characterized by adverse tissue reaction (see image below) and/or loose components. Soon clinical evidence made clear the full gravity of the situation.



Figure 2 – Adverse tissue reaction (metallosis) in a metal-on-metal hip (Pelt et al. e163).

In September 2008 (2 months after release in the US), the Australian Joint Registry reported high revision rates, and by 2010, the National Joint Registry (NJR) for England and Wales reported a 5 year revision rate (rate of reoperation for any reason) of 13% (more than 4 times higher than all other hip replacement devices combined) (Ardaugh, Graves, and Redberg 97-100). DePuy voluntarily recalled the ASR hip in 2010 after this rate was reported by NJR. Nearly 100,000 ASR hips were implanted worldwide before the product was recalled (Curfman and Redberg 975-77).

The ASR hip was cleared for sale by FDA without any clinical evidence. The ancestry of the predicate devices³ for ASR are documented by Argaugh (Ardaugh, Graves, and Redberg 97-100), revealing major flaws in the 510(k) process. The ancestry is traced back through 95 predicate devices. Many of these predicate devices are no longer in use because of a high rate of revision. Other orthopaedic companies have similar cases of high revision with their metal-on-metal hip products, and many of them have been recalled. Both FDA and the orthopaedic industry have

faced increasing scrutiny due to patient harm which resulted from the widespread use of metal-on-metal hip replacements.

Boneloc® Case Study

Another product that was marketed without any documentation of clinical performance was a bone cement called *Boneloc*. This new cement was created and marketed as a cold-curing cement that was less toxic to the surrounding bone (Nimb, Sturup, and Jensen 565-74). With standard bone cements, curing creates an exothermic reaction that produces heat and toxic chemicals (MMA monomer) and this can cause acute trauma to the surrounding bone. As Linder points out in his editorial in *Acta Orthopaedica Scandinavica* (Linder 205-06), “A reduction [in acute trauma] can do nothing but good, *everything else being equal*...The problem is that everything else is not equal. One cannot alter a single factor in bone cement – e.g., the exotherm – without also affecting other parameters.” The studies that were conducted before *Boneloc* was released were experiments in dogs with short-term follow-up in a non-weight-bearing situation (Linder 205-06).

After just a few years it became evident through the Norwegian Registry that *Boneloc* was inferior and its use was stopped in the country (Furnes et al. 515-20). The results were catastrophic for some. Nilsen and Wiig reported high rates of revision, radiographic signs of loosening, and osteolysis (degeneration or dissolution of the bone around the implant) in hips implanted with *Boneloc* cement (Nilsen and Wiig 57-59). Thanner et al., and Nilson and Dalen both showed *Boneloc* to be inferior with regards to migration (movement) of the implant in

randomized studies comparing Boneloc to another bone cement (Nilsson and Dalen 479-83;Thanner et al. 207-14).

This case study provides a few excellent questions regarding the development of new technology to help frame our discussion:

- 1) Was there a clinical need to develop new bone cement?
- 2) Was release of the product warranted without any clinical evidence in vivo to show its safety and effectiveness?

I would urge the reader to keep these questions in mind while reading the following pages.

Innovation must be pursued within the proper framework to be beneficial.

Historical Background

In the United States, the medical device industry is governed by the regulatory authority of the Center for Devices and Radiological Health (CDRH) of the Food and Drug Administration (FDA).

A medical device is defined by the FDA as “an instrument, apparatus, implement, machine, contrivance, implant, in vitro reagent, or other similar or related article, including a component part, or accessory which is:

- recognized in the official National Formulary, or the United States Pharmacopoeia, or any supplement to them
- intended for use in the diagnosis of disease or other conditions, or in the cure, mitigation, treatment, or prevention of disease, in man or other animals, or

- intended to affect the structure or any function of the body of man or other animals, and which does not achieve its primary intended purposes through chemical action within or on the body of man or other animals and which is not dependent upon being metabolized for the achievement of any of its primary intended purposes." (FDA n. pag.)

Medical device regulation is listed under 21 Code of Federal Regulations 812 (21 CFR 812), whereas pharmaceuticals are regulated by 21 CFR 312. Much of the regulation under 21 CFR governs both the drug and device industries – a few examples are listed below:

- Part 11 – Electronic Records
- Part 50 – Patient Informed Consent
- Part 54 – Financial Disclosure; and
- Part 56 – Institutional Review Boards (IRBs).

In 1938, the Food, Drug, and Cosmetic Act was passed. However, the regulation provided the FDA very limited power over medical devices and it was not until the Medical Device Amendments in 1976 that the FDA was given more regulatory oversight of the medical device industry. For more information, Susan Bartlett Foote provides an in-depth history of public policy evolution in the United States in the book: *Managing the Medical Arms Race* (Foote).

Over the years, the policy has been updated multiple times. The 1990 Safe Medical Devices Act gave the FDA more control over entry of new products into the market and in monitoring the use of marketed products (Merrill 47-69). The Medical Device User Fee and Modernization Act of 2002 established user fees for manufacturers for review of submissions and also set FDA performance targets for submission review times (Kramer, Xu, and Kesselheim 848-55).

Current Landscape

Devices that are manufactured for sale are classified into three categories based on risk classification determined by the level of control necessary to assure safety and efficacy. Class I devices are the lowest risk category and require general controls. Class II devices require general and special controls, and Class III devices require general controls and Premarket Approval. General controls are the FDA's baseline device requirements. Special controls are added requirements like performance standards and post-market surveillance that become necessary with the added level of risk. Premarket Approval is required of Class III devices because general and special controls are deemed to be insufficient to provide reasonable assurance of the safety and efficacy of the device (21CFR Part 814).

The regulatory pathway to which special attention is owed within this investigation is the 510(k). Products that are judged to be substantially equivalent to a product (or products) that have been previously cleared for sale in the United States are eligible to be regulated through 510(k). The device manufacturer must notify the FDA of intent to market a device at least 90 days in advance. If a device is brought to market through this pathway, it is subject to general and special controls, but clinical evidence of performance is not required before the product's widespread release to the public. Due to historical evidence like the ASR XL case study, it is clear that the widespread release of a faulty product can have devastating consequences. Also, many smaller countries place a high value on the FDA's decisions when making regulatory assessments, so the FDA's ruling has globally significant sway.

The FDA does not regulate the practice of medicine, so there is a gray area around issues like innovative surgical technique and the use of devices or drugs off-label (Eaton and Kennedy). These types of innovation are outside the scope of this project because the current regulatory structure in the United States is specifically designed to allow medical doctors the leverage to make decisions based on what they consider to be in the best interest of their patients. It is the innovation within device design and how regulatory structure helps guide its ethical release that will absorb our focus in the coming pages.

The Actors

The medical device industry is composed of four primary “actors.” For our purposes, these four actors will be labeled as the Manufacturer, Regulator, Provider, and Consumer. Each actor and their roles in the ethical implementation of innovation are described in more depth below. Later, when innovation is explored, the importance of innovation to each actor will also be examined.

Manufacturer

Definition & Scope

The manufacturer is responsible for creating the devices that seek to better the public’s quality of life. Diagnoses that would have been crippling as few as four decades ago are now successfully treated through medical devices that give patients mobility, that reduce or eliminate pain, and give back quality of life. From this perspective alone, the role of the manufacturer is vital to the process of bringing life-changing products to the consumer.

However, this role comes with responsibility, and the manufacturer of a device must embrace the responsibility of bringing safe and effective products to market. This is done through laboratory and clinical testing, a rigorous quality system that must extend throughout the organization and partnership with the other actors to fully understand how products are working in the patient.

Functions and Responsibilities

Ultimately, the manufacturer's responsibility lies in the creation of safe and effective devices. This responsibility is apparent within a company's development, marketing, regulatory, clinical, post-market surveillance, and quality functions. Ethical responsibilities are woven through these various functions. For instance, a company cannot use claims about a device in marketing without evidence (data) to back up that claim.

Barriers to Innovation

Regulation is often seen as a barrier to innovation for medical device manufacturers. If a truly new device is designed by a company, it may have to go through years of rigorous testing and clinical studies before the device can be marketed. Not only is the process time consuming, it is costly. Therefore, a company may have to make decisions relative to cost when deciding which new product development projects to pursue. It may ultimately choose less costly device modification projects (those that can go through a simpler regulatory process) compared with the big-idea projects that have potential spawn groundbreaking technology. This could certainly be seen as a barrier to innovation.

Ethical Considerations

The manufacturer is the first actor making choices at the ethical boundary. Costs are being weighed in device design, and at multiple points throughout the process. Ethical decisions will be made by those on the manufacturing floor as well as in the executive's office. Sometimes surgeons may be part of the development process, working with the manufacturer to create a device. These surgeons often receive royalty payments for this consultation. This creates another situation that is filled with ethical dilemmas, both on the part of the surgeon and the manufacturer. If the surgeon has opportunity to make large amounts of money off of the sale of a device (sometimes millions of dollars), will he or she be as willing to voice concern about safety issues, particularly if it is seemingly not being addressed by everyone else involved? Can a manufacturer leverage these relationships to get the answer it wants, even if legitimate concerns have been raised? The answer to both of these questions is likely yes, but the input of surgeons in the design process is invaluable, so it is probably a situation that should continue to be addressed and scrutinized, but not annihilated.

Corporations also have responsibilities to their shareholders which might pressure their ethical boundaries. Profit is gained through the sale of devices. New devices typically demand higher prices which makes the launch of new technology profitable. A rush to get new products to the market before the competition can lead to compromise of ethical values in an attempt to win in the world of business.

Clinical Landscape

Clinical performance data is necessary for determining the effectiveness of medical devices.

Data also needs to be collected in a timely and efficient manner after a product's release for it

to provide the most benefit in the case of unacceptable patient harm being determined after review of the data. In the case of ASR XL, nearly 100,000 patients were implanted with the faulty device before it was recalled by the company (Curfman and Redberg 975-77). If more rigorous clinical platforms had been in place to provide performance data for the device upon its release, the problem likely would have been more contained. Ultimately, the challenges are more complicated on a global scale, but this is a striking gap in the United States.

Clinical research is already an important component of regulatory submissions, both in the US and globally. However, devices often make it to the market with no clinical history required, and also, with no robust plan to be able to provide clinical data in a timely fashion after release. For instance, if a device is cleared through a 510(k) process with no requirements for clinical data, it may be years before any statistically significant data is available. It is likely the manufacturer intends to collect data, but how quickly will any problems be noticeable if an efficient, well planned study is not ready to be initiated directly after product launch? It is not the intention to blame the manufacturer for this gap. Clinical research is an important part of most companies, but when data is not required for marketing a product, or a clear plan for obtaining the data, the impetus for its collection falters, and funding is funneled elsewhere.

Randomized trials are typically seen as the “gold standard” within clinical research. Variability is decreased, the population needed for the study is typically lowered, and bias can be limited through blinding and the process of randomization itself. In medical device trials however, randomization is often difficult or impossible to implement for surgical intervention studies. In the instances when randomization can be used, patients are typically randomized into a group

to receive a standard-of-care device or a group to receive the study device. Randomized trials could be required within a step-wise regulatory approval process; a device might be granted limited approval for use in a short-term randomized study to test safety and effectiveness compared to a control (Stengel 85-91).

The United States does not have a national joint registry, which would aid in post-market surveillance activities to evaluate safety and effectiveness of products on the market. The Australian registry helped illuminate the safety concerns of the ASR hip. While a registry can be a powerful tool for surveillance of medical devices, it has limitations in being able to quickly highlight product safety issues which would need to be addressed through shorter-term studies aimed directly at predicting long-term outcomes (see discussion on RSA studies on page 39). This type of study might not exist for all device categories.

Regulator

Definition and Scope

The regulator of medical devices in the United States is the FDA (see page 12 above for more detail).

Functions and Responsibilities

The regulator serves as the oversight to the development, marketing, and sales of a device. Ultimately, the manufacturer needs to document and prove that established rules have been followed and they have completed the steps necessary to assess and reduce risk before launching a product. If this documentation is not clear, the regulator may step in with questions and suggestions for filling the gaps. In the event that a product is novel enough or risky enough

to fall outside of the 510(k) process, then extra oversight is provided through an Investigational Device Exemption (IDE)⁴ for submission of a Premarket Approval (PMA)⁵. This tightens regulatory requirements and requires at least 2 years of clinical data for a device. If a device is not working as intended, or is causing harm to patients at an unacceptable level, it is the responsibility of the regulator to step in and take action to remove the device from the market.

Barriers to Innovation

Regulation is not put in place to spark innovation but to provide a framework for its release to the public. Barriers to innovation within our regulatory framework in the United States typically revolve around inefficiencies in review of submissions for new devices. However, if the FDA must err on one side or another, I suppose the public benefits the most by an error toward caution. By allowing device modifications to be cleared through 510(k), the FDA might actually be stifling innovation by allowing products to be marketed without data to show safety and effectiveness. Innovation might actually benefit from stricter guidelines because manufacturers would be forced to more carefully consider the development of new products and in spending more time and money up-front with development and clinical research, innovation might flourish to a greater extent than it does now.

Ethical Considerations

Ethically, the FDA has an obligation to make its best effort to allow innovative devices to get to the consumer as quickly as possible, and to ensure to the best of its ability that the device is safe and effective for its intended use. This twofold ethical obligation is not easy to execute, making it almost impossible to succeed in everyone's estimation. The manufacturer can argue

that it is unethical to delay innovation to the marketplace while consumer advocates argue that pushing products to the market quickly is jeopardizing public safety.

Provider

The ethical responsibility rests heavily on the shoulders of the clinician to make a correct analysis of the need for a new product, before he begins to use it. If wrong, the patient has to pay the cost(Linder 205-06).

Definition and Scope

The provider includes both the hospital and the surgeon, who are responsible for treating a patient with medical devices. Ultimately, it is the provider who decides what device will be used for each case. In some instances the options may be very limited, but in others, like total hip and knee arthroplasty, there are a plethora of choices. Therefore, a provider must take their responsibility seriously and seek to limit any bias that might occur from relationships to a manufacturer. Hospitals and surgeons may often disagree on selected treatments (Healy and Iorio 57-63), but for the sake of this project we will oversimplify in viewing both entities as the same group.

The consumer, or patient, looks to their provider as the source they can trust for their treatment needs. The provider has to weigh multiple factors when selecting an appropriate treatment for a patient:

- 1) Clinical history - how the device has historically performed in clinical trials or in registries is one of the best ways a provider can make their decision.
- 2) Cost - how much a provider is willing to spend on a device is often a pressure that affects the selection of a device.

- 3) Benefit to the patient - if the device presents even the possibility of a greater benefit to the patient than others on the market it increases the likelihood that it will be selected.

Function and Responsibilities

The provider functions as the intermediary between the manufacturer and the patient. Medical device manufacturers, in some cases, have marketed directly to the consumer, but ultimately it is the surgeon (or hospital) that makes the final determination on treatment for their patients. Consumers are becoming more and more involved in their healthcare and have access to much information via the internet, but a vast majority of patients still trust their healthcare provider to select the right treatment for them, without any questioning of their judgment.

The provider is responsible to his or her client, the patient. Furthermore, the provider must follow regulations imposed for the use and sale of medical devices. In today's paradigm, it is not adequate for a surgeon or practitioner to merely act with a good conscience; it is necessary that all applicable laws and regulations are understood and followed. This is not necessarily an easy task. The regulations are massive, and many interpretations abound.

Barriers to Innovation

For the provider, cost may be a barrier to innovation. If a new technology is released, but the cost is prohibitive for sale in the hospital, then the surgeons practicing at that facility might not have access to that particular technology. Many hospitals are now requiring evidence to show that a new device warrants its higher price tag. Sometimes that evidence is not available if a technology has been approved without clinical evidence (such as through a PMA).

Ethical Considerations

Surgeons are often partners with the manufacture in innovation (Kesselheim, Xu, and Avorn e88664). They serve as consultants and designers, using their expertise in tandem with the resources of the manufacture to develop new products. This partnership provides value on many levels, but it also provides a potential for bias. When a surgeon helps design a product, it is likely that he/she will receive royalty payments for a percentage of the sales of that device. As a result, a conflict of interest is present for any surgeon who is receiving monetary gain for the sales of a device. Furthermore, a conflict of interest can be present through varying circumstances. Let's consider for a moment a surgeon who is paid by a medical device company for consulting. This surgeon travels across the world providing hands-on training for surgeons in residency programs at universities. Training is provided exclusively for one company and the surgeon is compensated well for his or her time. Alongside the money, the surgeon receives prestige as an expert within these educational and academic settings among his or her peers. This atmosphere can also create a conflict of interest, even if the money being provided is not directly attributed to sales of a particular device.

Consumer

Definition and Scope

The consumer, or patient, has an interesting role in the medical device arena. Usually the patient is not making a decision on what device they will receive during surgery, but companies in the United States have enacted "direct-to-consumer" marketing campaigns which attempt to plant a manufacturer's branding and therefore convey some of the impetus of device selection

to the patient. Patients also have opportunities, through media, to be more informed than ever regarding their medical care.

Functions and Responsibilities

The consumer is the end user of the device. The consumer is the patient who is placing trust in a hospital or a surgeon to provide adequate care. The patient should ask questions if they are uncomfortable with the care that they receive. However, oftentimes the patient does not have the appropriate knowledge to question a surgeon on any specific decisions being made in regard to their care. I have a scientific background and I do not feel qualified to question a medical doctor on most points regarding my medical care. This element of the unknown makes patients susceptible and vulnerable to agreeing to more risk than they realize they are accepting. For instance, a patient can be asked to participate in a research study and sign an informed consent after being provided time to read through study procedures and ask questions of the surgeon, without fully understanding the scope of the research that they are submitting to. In the end, they are placing trust in their surgeon's description, demeanor, and guidance in agreeing to the study. A similar situation can occur with device selection. The patient often has to fully trust the surgeon's risk assessment in selecting the product.

Barriers to Innovation

A major barrier to innovation for the consumer is cost. It is difficult to encourage technological innovation in the medical sector and not drive up costs. Models have been proposed which seek to incentivize both increased technological innovation and reduced cost (Gelijns and Rosenberg 28-46; Rettig 7-27), but this has not been attained. The United States is a marketplace that pays well for healthcare. This makes it a desirable place to conduct business

and therefore, many products are available to the public. However, as costs continue to rise, a solution is needed for this dilemma. This problem is outside the scope of the current project, but evidence-based medicine and a change in regulatory structure could aid in shifting how the United States reviews and processes innovation to move toward a more value-based decision structure for the selection and implementation of devices (Obremskey, Dail, and Jahangir 1054-64; Healy and Iorio 57-63; Ranawat, Nunley, and Bozic 2556-60; Lansky and Milstein 2548-55).

Ethical Considerations

The patient must be able to rely on his or her provider for treatment. Transparency is a must when discussing a treatment and potential alternatives. That is why conflict of interest is such an important topic. A patient should know how conflicted their provider is. Conflict of interest is unavoidable, but it does present interesting ethical situations and opportunities for bias. The US recently passed a law to require reporting of payments from drug and device companies to physicians (Steinbrook 2160-63; Woodward E467-E468). Some physicians are being paid millions of dollars per year for consulting and royalties. While this does not automatically suggest unethical behavior, it certainly raises concern for bias in prescribing treatment and overseeing clinical activities. It is important that these concerns are raised with patients in the course of their treatment as well, so the patient has full disclosure.

Actor Relationships

Above I reviewed each of the actors within a vacuum. That is, I ignored the relational reality so necessary to fully understand the environment in which decisions are made. In following sections I will briefly discuss how the actors work together to innovate and the ethical

considerations woven throughout these interactions. A flowchart attached below (Appendix B) gives a brief glimpse of how the actors' roles are married throughout the device lifecycle.

Ethics in the Medical Device Industry

While it is probably true that all doctors, scientists and engineers design and implement medical devices with only good intentions, the rapid pace of their development and integration into medical practice and other areas of health care makes it impossible to anticipate all the possible consequences that may result from their use (Gelijns, Rosenberg, and Moskowitz 693-98).

The primary focus in the medical device industry must be the rights and safety of the patient.

History provides many examples of egregiously unethical behavior toward the human race in the name of science (Jones;Spitz). This unjust behavior has sparked the creation of ethical codes like the Nuremburg Code and the Declaration of Helsinki (see Appendix A). These codes, along with medical device regulation and other standards for good clinical practice (Belmont Report, ISO 14155, ICH E6) help guide the ethical conduct of human clinical trials.

As described above (page 23), conflict of interest is an ethical concern within the medical device industry. Gelberman et al. describe it as a “threat to scientific integrity and the public trust” (Gelberman et al. 765-77). Bias in research, clinical evaluations, and treatment does indeed threaten the integrity of results. It is common for investigators of a clinical trial to disclose conflicts of interest (Lo, Wolf, and Berkeley 1616-20), but what disclosure is owed to the patient? Many reports and recommendations have called for increased scrutiny and transparency of payments (Steinbrook 2160-63), but the transparency needs to be present in the relationship between surgeon and patient for it to be meaningful. It is a step in the right direction for conflict of interest to be listed in medical journals, presentations and websites, but

ultimately the patient needs to understand the potential bias that conflict of interest can create and be able to evaluate its risk in their personal medical treatment.

Ethical decisions are faced outside of human clinical trials. Ethics should guide and shape everything from product design to regulations to post-market surveillance activities. The difficulty is captured in the quote introducing this section. It may be impossible to anticipate all possible consequences of device innovation, but risk should be properly assessed and regulation should provide adequate structure for ethically introducing new technology to the market.

The question should be asked: what can stop situations like the metal-on-metal hip failures from happening again? Stopping all device failure is impossible. Stopping all device design failures from being released to the public is also too lofty a goal. However, what about limiting the scope of the failure? What if we could catch and limit failures earlier so fewer have to suffer? This possibility is very much within our reach.

Regulation in the United States should provide a paradigm that allows manufacturers to cost-effectively bring new and innovative products to market while protecting the safety and well-being of the public. It can also be argued that it is the responsibility of the provider and the manufacturer to attempt to limit cost for the public. Kriewall suggests that “medical device manufacturers face challenges as they strive to offer the ultimate in product safety and keep the price affordable for the technology deployed, while making the usability of typically complex products common sense for the operator”(Kriewall 167-74).

Everyone involved in medical device manufacturing should value the ethical responsibility that is owed to the patient. However, we must succeed in bettering our processes to more effectively serve public need.

Innovation in the Medical Device Industry

Innovation can be defined as a new idea, device, or process. The innovation that is sought in the medical device industry is better than the existing standard of care. To simply create something novel that fails is not worth calling innovation. Furthermore, to create a product that offers no gain in success compared to existing products is not innovation. Not every idea will succeed, and the innovative process needs room for error. However, the system in place should block the progress, release, and creation of failed innovation most of the time. The rest of the time the failure should be curtailed by regulation and strict post-market follow-up procedures.

According to Foote (Foote), the stages of innovation within the medical device industry can be broken down into the following: discovery and distribution, with the newly created product falling between each stage (see Figure 3 below).

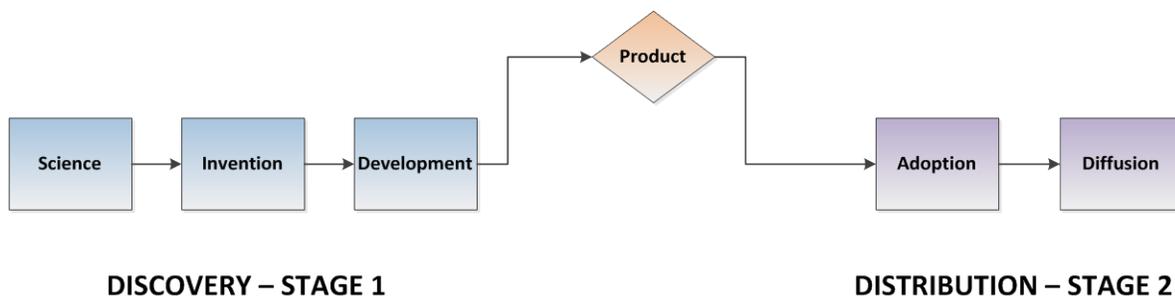


Figure 3 – adapted from *Managing the Medical Arms Race* (Foote).

Checks need to be in place during and between each stage to help limit flawed product from being fully diffused into the public. These checks guide design, the assessment of risk, and product release, among other steps along the way. We should use situations like the case studies presented earlier to alert us to the need for change and enact such change before a similar situation occurs again.

Levels of Innovation

Innovation occurs to in varying degree. Innovation does not always create an unrecognizable product that rocks the industry. Typically, change happens through small modifications to existing designs. These modifications, though relatively small, can affect major change in performance – positive and negative. Generally, innovation can be defined as incremental, substantial, or radical.

Level I – Incremental

Strangely enough, incremental change to medical devices has more potential to cause harm to the public than substantial or radical innovation, because these changes can still be approved without any clinical performance data. Incremental innovation *typically* does not cause safety concern. However, there are cases in which minor modification decreases performance or causes failure of the device. It is these cases that have led to a call for a new paradigm for the regulation of incremental innovation (Nieuwenhuijse et al. g5133;Kesselheim and Rajan g5303).

Level II – Substantial

Substantial innovation gives a company competitive advantage with the creation of technology that moves the industry forward with “best-in-class” products. This level of innovation might

still be cleared through 510(k). If the device can still be claimed as substantially equivalent to a predicate device, even if the innovation is substantial, there is potential for it to be sold in without clinical performance data being required.

Level III – Radical

Radical innovation is the creation of a product or process that is startlingly progressive. It will be recognized outside the industry (sometimes it will come from outside the industry) for its novelty and ability to create new norms or standards of care. This level of innovation will require a PMA application and an IDE. Therefore, it is unlikely that radical innovation could cause a significant level of harm in the United States population, and will therefore not be addressed in the suggested changes soon to be discussed.

Difference between Sustaining and Disruptive Innovations

There is also a difference between sustaining and disruptive innovation in the medical device industry. Sustaining innovation is the level that draws the most focus from industry. To sustain a competitive place in the market, companies pour high levels of resources into their current products and services to continue meeting the needs of their customers. Disruptive innovation refers to the creation of cheaper, simpler, more convenient products which alter the course of the industry by eventually meeting the needs of a large majority of the population. Christensen et al. argue strongly for allowing disruptive innovation in healthcare to “build a new system that’s characterized by lower costs, higher quality, and greater convenience than could ever be achieved under the old system.” The authors also challenge regulators to “enable disruptive innovations to emerge” (Christensen, Bohmer, and Kenagy 102-12, 199). If disruptive

innovation truly can provide lower costs and higher quality to the patient, it should be an ethical imperative to allow it in the healthcare marketplace and each of us should challenge the status quo to help enact such a change.

Multiple recent symposia have been held to discuss the optimum method for introduction of new technologies into the public (Callaghan et al. 1146-58; Jacobs et al. 1650-63). The issue is even more relevant in the midst of the failures of products like metal-on-metal hips. Models for graduated introduction of medical devices have been suggested (Zywiell, Johnson, and Monte158; Malchau, Bragdon, and Muratoglu 825-31; Malchau 285). These models seek to encourage limited release of medical devices in a step-wise fashion to more safely introduce new technology. I am in favor of such an approach and it will be discussed in more depth in recommending revision of current 510(k) policy.

Why is Innovation Important?

Manufacturer Mindset

Innovation is the key to driving and sustaining growth for medical device manufacturers. New and innovative products drive sales. Companies desire innovation that will set them apart from their competition and draw the attention of the provider. Sometimes this constant push for innovation, however, can be dangerous. If a company pushes too hard to get a product to the market without doing everything it can to verify its safety and effectiveness, an unsafe or ineffective product could be released. However, typically it is the belief of the manufacturer (speaking in general of course) that the regulatory machinery hinders innovation and makes its

release to market too costly and time-consuming. If life-saving or life-altering products are delayed by too strict a regulatory process, then ultimately it is the patient that loses.

Regulator Mindset

The government is in a difficult place as well when it comes to innovation. Certainly they would like to bring products that benefit the public to market as quickly as possible. However, they also face criticism when mistakes happen. All of the other actors may pressure the FDA, but it is ultimately the FDA's goal to provide the public with access to innovation, since the department was created to serve the consumer. Risk and benefit have to be weighed, which takes time, energy, and money. Recently the FDA has attempted to process PMA applications for new devices more quickly by increasing user fees paid by industry for regulatory reviews.

Provider Mindset

For a provider, innovative products mean better results for patients. This is valuable to the hospital and surgeon both for providing beneficial service to the patient and in increasing the opportunity for financial gain. However, even if patient care is the primary focus of all providers, the financial impetus cannot be denied. Money is in the background (some might say at the forefront) of all healthcare transactions, even in the most protected scenarios where providers attempt to hold bias and improper influence in check. Innovation and new technology almost always comes with increased cost in the United States.

Consumer Mindset

For the consumer, innovation is a better outcome (theoretically). As the population ages, yet retains expectations of maintaining an active lifestyle, innovation becomes even more

important. Patients might be willing to take on the higher risk that comes with the use of a new product if it means the possibility of a superior result. However, this risk must be mitigated to ethically provide new technology to the public.

Optimizing Innovation

What is the need for optimization? (What isn't working?)

Optimizing innovation does not necessarily mean faster innovation. Truly optimized innovation in the medical device industry will include a balance of regulation, quality systems, design interaction between multiple parties, documentation of rationale, ethical considerations, clinical follow-up, post-market surveillance, informed patient consent, and many other factors. Cross-functional teamwork and at least some understanding about how all the individuals work together to invent, manufacture, sell, provide, consume, and monitor a medical device – all within an ethical framework – will go far in optimizing the process of innovation. As discussed above, all actors involved have strong motivation to see truly innovative products become available to the public as quickly as possible. On the other hand, each actor has faced the reality of failure.

When innovation “goes wrong,” all parties suffer. When honest and open dialogue is not occurring and actors are fighting for their own interests above all else, innovation is hindered. Each actor has a part to play, and the part is vital to the whole. The manufacturer must provide profit for its stakeholders, but has to rely on the provider and regulator to do so, and must serve the consumer. If each actor works in a vacuum and sees the others as a means to their

own goals, without regard to the worth of each, innovation will stagnate. I believe each actor realizes this and attempts to legitimately learn and understand the others for the benefit of all, but this is not an easy task. The actors are made up of multiple companies, branches, advocacy groups, departments, specialties, practices, careers, educational backgrounds, etc. An even further complication is that each individual offers differing perspective within the broader “institutional” scope.

Clear and meaningful communication is necessary for furtherance of innovation within an ethical framework. All parties must converge on singular goals for providing new technology to the public in a way that maximizes benefits and squashes risk. If policy is failing to provide adequate oversight and guidelines to do this, we must push for policy that more adequately provides framework to ethically design and release innovative new technology.

Manufacturer Mindset

The manufacturer’s reputation is likely most at stake among the actors if innovation does indeed fail. On the other hand, their financial reward is probably the greatest when innovation succeeds. The faster a new product is marketable, the faster a company can profit. If a company has to go through lengthy regulatory processes, including clinical studies, to get a device on the market, profit margins are compromised. Therefore, it makes sense that manufacturers will often go through the least burdensome process that is legally acceptable to sell a product. The system works most of the time, and the field of medicine continues to surge forward. However, when failure happens, the manufacturer’s reputation is tarnished. Not only does the product and company get splashed across the headlines, but litigation ensues and costly legal battles

are waged. This is the climate in the United States. Johnson & Johnson has spent billions of dollars settling cases and paying legal fees to fight litigation for the ASR hip. Therefore, it is in the manufacturer's best interest that we progress to develop a system that more effectively eliminates these catastrophic and widespread failures.

Regulator Mindset

The FDA's reputation is also tarnished when cleared or approved devices fail. The regulatory process is questioned and fixes are suggested or demanded to improve patient safety. It is important to note, however, that risk in the medical device industry will never be eliminated. Risk can only be mitigated and weighed against benefit. The vast majority of medical devices work wonders in improving the lives of their recipients, but a percentage of devices fail. The root cause of failure is not always easy to pinpoint. Devices can fail for a wide variety of reasons: user error or improper surgical technique, poor design, patient co-morbidities, or inadequate or non-compliant post-surgical protocol. However, the regulator is responsible for ensuring that device design is not flawed. The FDA does this by requiring that manufacturers create devices that they deem substantially equivalent to existing products or by going through a more lengthy premarket approval submission which requires clinical data to show safety and efficacy of a product before its release.

The FDA's reputation is also questioned when release of innovation is delayed. Pressure can come from all the actors. Ultimately, patient safety has to be the foremost concern, regardless of the pressure coming from outside sources. However, the FDA realizes the need to be efficient in their review and pushes for increased funding and resources from both the United

States government and from manufactures through increased review fees to keep up with increased workload and keep review times reasonable.

Provider Mindset

The provider faces pressure from the manufacturer and from the consumer to provide the newest and best products. The manufacturer pushes for premium (higher) pricing for new products and the consumer wants “cutting-edge” technology which is often considered to be the best. A recent study showed that trust for medical professionals is waning (Blendon, Benson, and Hero 1570-72), making it more difficult for surgeons to make unquestioned decisions in the best interest of their patients. This is both positive and negative. Patients should take an active interest in their healthcare, but they also need to know what questions to ask and what is in their best interest, so they can accurately question their clinician and develop trust.

Consumer Mindset

What is the value of a new technology? How is the potential value weighed against the potential risk? Is it worth it to try new technology if there are well-performing alternatives on the market? Is the potential for slightly improved outcomes worth passing up a time-tested device that has years of positive clinical history? Each individual is different and may have vastly diverse answers to these questions. For surgeons and patients, some are more comfortable than others in assuming risk, which is why it is important that a patient knows what risk he or she is assuming with the device in question. Having options for the patient seems reasonable – a new device that offers a potential for superior results versus a standard-of-care device that

has good clinical history but may not be able to offer hope for better results. Do patients really have that choice? Or does the surgeon have full control over selection of the implant? From an ethical standpoint, the patient should have a voice in the decision being made, particularly in reference to the risk being assumed.

Novel Approaches

Improving or Redefining the 510(k) Submission Process

Hillman argued that government health policy was ineffectual for the appropriate diffusion of cost-effective medical devices less than a decade after the Medical Device Amendments in 1976 (Hillman 681-711). Recently, 510(k) legislation was called into question by an Institute of Medicine report which concluded the same and recommended that the FDA design a new regulatory framework for Class II device approval (Institute of Medicine; Challoner and Vodra 977-79).

The 510(k) process needs revision. I do not propose an overhaul to the entire system – particularly not at one time – but something has to change in light of the case studies described above and others like them. Currently the 510(k) submission process allows products to be marketed based primarily on a verification of a manufacturer's claim(s) of substantial equivalence to other legally marketed devices. These predicates do not have to be clinically proven devices; they only have to be legally marketable.

On the other hand, it is beneficial that not every device is required to go through a lengthy and costly PMA. However, it is irresponsible and unethical to allow devices in the marketplace

without clinical history. Instead of allowing substantial equivalence to be claimed to any existing device that was previously cleared, wouldn't it make sense to only allow this equivalence to be tied to existing devices with adequate clinical performance? This seemingly minor distinction would still allow manufacturers to show a device to be similar enough to an existing device in order to warrant simpler regulatory pathways, but with the stipulation that the device they compare to has proven *positive* clinical performance.

Along with the stipulation above, I think the post-market surveillance of 510(k) cleared products should be more rigorous. The manufacturer should have to plan ahead for how a device's clinical history will be studied, tracked, and monitored for possible safety concerns upon release.

This proposed change fits nicely with the FDA's current system for Class III devices which often require Post-Approval Studies to collect long term data on safety and effectiveness, even after a device has been awarded approval through a PMA. Class II devices would have similar requirements for the collection of clinical performance data after release, but would still be allowed on the market without rigorous up-front human clinical trials.

The manufacturer might balk at this proposed change. However, in many ways this is already the expectation. Ethically, it is the manufacturer's responsibility to choose a predicate that is a properly functioning device. Such a device should have a positive clinical performance history (the author does realize that a clinical gap is likely present for many devices) which would already be included in today's 510(k) submissions. The manufacturer should also be employing post-market surveillance on its products. However, it may often be the case that the

surveillance is not robust enough, or is not started quickly enough to be properly effective in catching any problems.

Under this paradigm shift, therefore, the manufacturer would have to plan adequately before launching new innovation to account for these requirements. Clinical studies would need to be ready to start shortly after a device was released so data on early cases could be collected and analyzed before large numbers of patients receive the device. Also, special emphasis should be placed on short-term studies that can predict long-term outcomes, such as Radiostereometric Analysis (RSA) (Karrholm, Gill, and Valstar 10-21; Nelissen et al. 62-65). For some orthopaedic surgery applications, RSA has been shown to be an accurate predictor of long-term results for implant fixation, and because the technology is so precise, typically statistically significant results can be acquired with smaller numbers of study patients.

Role of Universal Health Care

The Affordable Care Act is just beginning to change the landscape of healthcare in the United States. There are still many unknowns and it is difficult to predict exactly what affect the law will have on healthcare as a whole, and the medical device industry specifically. It may provide opportunity for increased standardization for medical device companies with how devices are approved for market, sold, and how clinical performance data is tracked. Model-based evaluations would be a way to standardize reporting, assess cost and complications and inform creation of robust post-market surveillance plans (Suter et al. 1464-66). A standardized health structure in the United States would help with these efforts to provide safe, well-performing and cost-effective medical device solutions.

National Registry

There is a lack of publicly available data on implanted medical devices (Zuckerman, Brown, and Das 1781-87). Without data, how can safety assessments be made with any confidence? A national registry would help solve this issue in the United States. Registries in Australia, and England and Wales were the first to indicate problems with metal-on-metal hips years ago. Even though a registry would not provide newly released device safety information quickly, it could be used in tandem with strategic post-market clinical studies to identify safety concerns (Nelissen et al. 62-65).

Consumer First Mentality

Consumers are a force in healthcare (Herzlinger 58-66, 156). The changing landscape reveals patients who are not only paying more attention to healthcare issues; they are paying tremendous amounts of money for their care. Leveraging this shift, the other actors should help empower patients in healthcare decisions to move innovation forward. This should be done for the benefit of the patient, not as a sales and marketing tactic. As consumers pay more for their care, they will likely be more and more involved in weighing the appropriateness of a new technology for their specific needs.

Conclusion

There is not an easy fix for more effectively regulating medical devices to ethically allow the introduction of innovation into the public. However, the current system has flaws which need to be addressed, even if it is unwieldy to reform the entire system. Ultimately, the course that

best protects the interests of the public, which is a course with a weighty pull from many sides, is where we must proceed. Just like device companies slightly modify existing products to make them more effective, regulations can be innovatively modified to provide a better ethical framework for providing medical device innovation to the public.

Notes

1. A Premarket Notification [510(k)] is a submission made to the FDA before marketing of a device to prove substantial equivalence (SE) to a previously marketed device and, in theory, the safety and effectiveness of the device.

<http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/HowtoMarketYourDevice/Pre-marketSubmissions/PremarketNotification510k/ucm134571.htm>

2. Johnson and Johnson agreed to a settlement as large as \$4 billion to settle thousands of lawsuits filed by those injured by the ASR XL metal-on-metal hip (Meier). Drug companies have also paid huge settlements for injuries caused by faulty products: Yasmin (Bayer) - \$110 million; Prempro (Pfizer) - \$330 million; Avandia (GlaxoSmithKline) - \$460 million; Vioxx (Merck) – \$4.85 billion (Drug and Medical Device Lawsuits).

3. A predicate device is a legally marketed device to which equivalence is drawn in a Premarket Notification [510(k)] submission. Any legally marketed device can be claimed as a predicate.

<http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/HowtoMarketYourDevice/Pre-marketSubmissions/PremarketNotification510k/ucm134571.htm>

4. An Investigational Device Exemption (IDE) allows an investigational device to be used in a clinical study in order to collect data to show safety and effectiveness.

<http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/HowtoMarketYourDevice/InvestigationalDeviceExemptionIDE/default.htm>

5. A Premarket Approval (PMA) is essentially a private license to market and sell a Class III medical device. It is the equivalent of a New Drug Application (NDA) in the pharmaceutical regulation.

<http://www.fda.gov/MedicalDevices/ProductsandMedicalProcedures/DeviceApprovalsandClearances/PMAApprovals/default.htm>

Reference List

- Drug and Medical Device Lawsuits. <http://www.drugwatch.com/drug-lawsuits.php> . 9-23-2014.
- Ardaugh, B. M., S. E. Graves, and R. F. Redberg. "The 510(k) ancestry of a metal-on-metal hip implant." N.Engl.J.Med. 368.2 (2013): 97-100.
- Blendon, R. J., J. M. Benson, and J. O. Hero. "Public trust in physicians--U.S. medicine in international perspective." N.Engl.J.Med. 371.17 (2014): 1570-72.
- Callaghan, J. J., et al. "Symposium: introducing technology into orthopaedic practice. How should it be done?" J.Bone Joint Surg.Am. 87.5 (2005): 1146-58.
- Challoner, D. R. and W. W. Vodra. "Medical devices and health--creating a new regulatory framework for moderate-risk devices." N.Engl.J.Med. 365.11 (2011): 977-79.
- Christensen, C. M., R. Bohmer, and J. Kenagy. "Will disruptive innovations cure health care?" Harv.Bus.Rev. 78.5 (2000): 102-12, 199.
- Curfman, G. D. and R. F. Redberg. "Medical devices--balancing regulation and innovation." N.Engl.J.Med. 365.11 (2011): 975-77.
- Daniel, J., P. B. Pynsent, and D. J. McMinn. "Metal-on-metal resurfacing of the hip in patients under the age of 55 years with osteoarthritis." J.Bone Joint Surg.Br. 86.2 (2004): 177-84.

Eaton, ML and Kennedy, D. Innovation in Medical Technology. Ethical Issues and Challenges.
2007. The Johns Hopkins University Press.

FDA.

<http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/Overview/ClassifyYourDevice/ucm051512.htm>. n. pag. 2014.

Foot, Susan Bartlett. Managing the Medical Arms Race: Public Policy and Medical Device
Innovation. 1992. University of California Press.

Furnes, O., et al. "Exeter and Charnley arthroplasties with Boneloc or high viscosity cement.
Comparison of 1,127 arthroplasties followed for 5 years in the Norwegian Arthroplasty
Register." Acta Orthop.Scand. 68.6 (1997): 515-20.

Gelberman, R. H., et al. "Orthopaedic surgeons and the medical device industry: the threat to
scientific integrity and the public trust." J.Bone Joint Surg.Am. 92.3 (2010): 765-77.

Gelijns, A. and N. Rosenberg. "The dynamics of technological change in medicine." Health
Aff.(Millwood.) 13.3 (1994): 28-46.

Gelijns, A. C., N. Rosenberg, and A. J. Moskowitz. "Capturing the unexpected benefits of medical
research." N.Engl.J.Med. 339.10 (1998): 693-98.

Green, S. A. "The evolution of medical technology: lessons from the Burgess Shale."
Clin.Orthop.Relat Res. 385 (2001): 260-66.

Healy, W. L. and R. Iorio. "Implant selection and cost for total joint arthroplasty: conflict
between surgeons and hospitals." Clin.Orthop.Relat Res. 457 (2007): 57-63.

Herzlinger, R. E. "Why innovation in health care is so hard." Harv.Bus.Rev. 84.5 (2006): 58-66, 156.

Hillman, B. J. "Government health policy and the diffusion of new medical devices." Health Serv.Res. 21.5 (1986): 681-711.

Huiskes, R. "Failed innovation in total hip replacement. Diagnosis and proposals for a cure." Acta Orthop.Scand. 64.6 (1993): 699-716.

Institute of Medicine. Medical devices and the public's health: the FDA 510(k) clearance process at 35 years. Washington, DC, National Academies Press.

Jacobs, J. J., et al. "Relationships with industry: critical for new technology or an unnecessary evil?" J.Bone Joint Surg.Am. 88.7 (2006): 1650-63.

Jones, James H. Bad Blood: The Tuskegee Syphilis Experiment. 1992. Free Press.

Karrholm, J., R. H. Gill, and E. R. Valstar. "The history and future of radiostereometric analysis." Clin.Orthop.Relat Res. 448 (2006): 10-21.

Kesselheim, A. S. and P. V. Rajan. "Regulating incremental innovation in medical devices." BMJ 349 (2014): g5303.

Kesselheim, A. S., S. Xu, and J. Avorn. "Clinicians' contributions to the development of coronary artery stents: a qualitative study of transformative device innovation." PLoS.One. 9.2 (2014): e88664.

Kramer, D. B., S. Xu, and A. S. Kesselheim. "Regulation of medical devices in the United States and European Union." N.Engl.J.Med. 366.9 (2012): 848-55.

Kriewall, T. J. "Ethics of medical device safety." J.Long.Term.Eff.Med.Implants. 18.2 (2008): 167-74.

Lansky, D. and A. Milstein. "Quality measurement in orthopaedics: the purchasers' view." Clin.Orthop.Relat Res. 467.10 (2009): 2548-55.

Linder, L. "Boneloc--The Christiansen experience revisited." Acta Orthop.Scand. 66.3 (1995): 205-06.

Lo, B., L. E. Wolf, and A. Berkeley. "Conflict-of-interest policies for investigators in clinical trials." N.Engl.J.Med. 343.22 (2000): 1616-20.

Malchau, H. "Introducing new technology: a stepwise algorithm." Spine (Phila Pa 1976.) 25.3 (2000): 285.

Malchau, H., C. R. Bragdon, and O. K. Muratoglu. "The stepwise introduction of innovation into orthopedic surgery: the next level of dilemmas." J.Arthroplasty 26.6 (2011): 825-31.

Meier, Barry. Johnson & Johnson Said to Agree to \$4 Billion Settlement Over Hip Implants. New York Times [<http://www.nytimes.com/2013/11/13/business/johnson-and-johnson-said-to-agree-to-4-billion-settlement-over-hip-implants.html>]. 11-12-2014.

Merrill, R. A. "Regulation of drugs and devices: an evolution." Health Aff.(Millwood.) 13.3 (1994): 47-69.

Nelissen, R. G., et al. "RSA and registries: the quest for phased introduction of new implants."

J.Bone Joint Surg.Am. 93 Suppl 3 (2011): 62-65.

Nieuwenhuijse, M. J., et al. "Appraisal of evidence base for introduction of new implants in hip and knee replacement: a systematic review of five widely used device technologies."

BMJ 349 (2014): g5133.

Nilsen, A. R. and M. Wiig. "Total hip arthroplasty with Boneloc: loosening in 102/157 cases after

0.5-3 years." Acta Orthop.Scand. 67.1 (1996): 57-59.

Nilsson, K. G. and T. Dalen. "Inferior performance of Boneloc bone cement in total knee

arthroplasty: a prospective randomized study comparing Boneloc with Palacos using radiostereometry (RSA) in 19 patients." Acta Orthop.Scand. 69.5 (1998): 479-83.

Nimb, L., J. Sturup, and J. S. Jensen. "Improved cortical histology after cementation with a new

MMA-DMA-IBMA bone cement: an animal study." J.Biomed.Mater.Res. 27.5 (1993): 565-74.

Obremskey, W. T., T. Dail, and A. A. Jahangir. "Value-based purchasing of medical devices."

Clin.Orthop.Relat Res. 470.4 (2012): 1054-64.

Pelt, C. E., et al. "Histologic, serologic, and tribologic findings in failed metal-on-metal total hip

arthroplasty: AAOS exhibit selection." J.Bone Joint Surg.Am. 95.21 (2013): e163.

Ranawat, A. S., R. Nunley, and K. Bozic. "Executive summary: value-based purchasing and

technology assessment in orthopaedics." Clin.Orthop.Relat Res. 467.10 (2009): 2556-60.

Rettig, R. A. "Medical innovation duels cost containment." Health Aff.(Millwood.) 13.3 (1994): 7-27.

Spitz, Vivian. *Doctors from Hell: The Horrific Account of Nazi Experiments on Humans.* 2014. Sentient Publications.

Steinbrook, R. "Controlling conflict of interest--proposals from the Institute of Medicine." N.Engl.J.Med. 360.21 (2009): 2160-63.

Stengel, D. "The changing landscape of product development and randomized trials." J.Bone Joint Surg.Am. 94 Suppl 1 (2012): 85-91.

Suter, L. G., et al. "Medical device innovation--is "better" good enough?" N.Engl.J.Med. 365.16 (2011): 1464-66.

Thanner, J., et al. "Evaluation of Boneloc. Chemical and mechanical properties, and a randomized clinical study of 30 total hip arthroplasties." Acta Orthop.Scand. 66.3 (1995): 207-14.

Woodward, C. "New US law applies 'sunshine' to physician payments and gifts from drug, device industries." CMAJ. 182.10 (2010): E467-E468.

Zuckerman, D., P. Brown, and A. Das. "Lack of Publicly Available Scientific Evidence on the Safety and Effectiveness of Implanted Medical Devices." JAMA Intern.Med. 174.11 (2014): 1781-87.

Zywiell, M. G., A. J. Johnson, and M. A. Mont. "Graduated introduction of orthopaedic implants: encouraging innovation and minimizing harm." J.Bone Joint Surg.Am. 94.21 (2012): e158.

Appendix A: Nuremburg Code & Declaration of Helsinki

Nuremberg Code

The great weight of the evidence before us is to the effect that certain types of medical experiments on human beings, when kept within reasonably well-defined bounds, conform to the ethics of the medical profession generally. The protagonists of the practice of human experimentation justify their views on the basis that such experiments yield results for the good of society that are unprocurable by other methods or means of study. All agree, however, that certain basic principles must be observed in order to satisfy moral, ethical and legal concepts:

1. The voluntary consent of the human subject is absolutely essential.

This means that the person involved should have legal capacity to give consent; should be so situated as to be able to exercise free power of choice, without the intervention of any element of force, fraud, deceit, duress, over-reaching, or other ulterior form of constraint or coercion; and should have sufficient knowledge and comprehension of the elements of the subject matter involved as to enable him to make an understanding and enlightened decision. This latter element requires that before the acceptance of an affirmative decision by the experimental subject there should be made known to him the nature, duration, and purpose of the experiment; the method and means by which it is to be conducted; all inconveniences and hazards reasonably to be expected; and the effects upon his health or person which may possibly come from his participation in the experiment.

The duty and responsibility for ascertaining the quality of the consent rests upon each individual who initiates, directs or engages in the experiment. It is a personal duty and responsibility which may not be delegated to another with impunity.

2. The experiment should be such as to yield fruitful results for the good of society, unprocurable by other methods or means of study, and not random and unnecessary in nature.

3. The experiment should be so designed and based on the results of animal experimentation and a knowledge of the natural history of the disease or other problem under study that the anticipated results will justify the performance of the experiment.

4. The experiment should be so conducted as to avoid all unnecessary physical and mental suffering and injury.

5. No experiment should be conducted where there is an a priori reason to believe that death or disabling injury will occur; except, perhaps, in those experiments where the experimental physicians also serve as subjects.

6. The degree of risk to be taken should never exceed that determined by the humanitarian importance of the problem to be solved by the experiment.
7. Proper preparations should be made and adequate facilities provided to protect the experimental subject against even remote possibilities of injury, disability, or death.
8. The experiment should be conducted only by scientifically qualified persons. The highest degree of skill and care should be required through all stages of the experiment of those who conduct or engage in the experiment.
9. During the course of the experiment the human subject should be at liberty to bring the experiment to an end if he has reached the physical or mental state where continuation of the experiment seems to him to be impossible.
10. During the course of the experiment the scientist in charge must be prepared to terminate the experiment at any stage, if he has probably cause to believe, in the exercise of the good faith, superior skill and careful judgment required of him that a continuation of the experiment is likely to result in injury, disability, or death to the experimental subject.

WMA Declaration of Helsinki - Ethical Principles for Medical Research Involving Human Subjects

Adopted by the 18th WMA General Assembly, Helsinki, Finland, June 1964
and amended by the:

29th WMA General Assembly, Tokyo, Japan, October 1975

35th WMA General Assembly, Venice, Italy, October 1983

41st WMA General Assembly, Hong Kong, September 1989

48th WMA General Assembly, Somerset West, Republic of South Africa, October 1996

52nd WMA General Assembly, Edinburgh, Scotland, October 2000

53rd WMA General Assembly, Washington DC, USA, October 2002 (Note of Clarification added)

55th WMA General Assembly, Tokyo, Japan, October 2004 (Note of Clarification added)

59th WMA General Assembly, Seoul, Republic of Korea, October 2008

64th WMA General Assembly, Fortaleza, Brazil, October 2013

Preamble

1. The World Medical Association (WMA) has developed the Declaration of Helsinki as a statement of ethical principles for medical research involving human subjects, including research on identifiable human material and data.

The Declaration is intended to be read as a whole and each of its constituent paragraphs should be applied with consideration of all other relevant paragraphs.

2. Consistent with the mandate of the WMA, the Declaration is addressed primarily to physicians. The WMA encourages others who are involved in medical research involving human subjects to adopt these principles.

General Principles

3. The Declaration of Geneva of the WMA binds the physician with the words, "The health of my patient will be my first consideration," and the International Code of Medical Ethics declares that, "A physician shall act in the patient's best interest when providing medical care."

4. It is the duty of the physician to promote and safeguard the health, well-being and rights of patients, including those who are involved in medical research. The physician's knowledge and conscience are dedicated to the fulfilment of this duty.

5. Medical progress is based on research that ultimately must include studies involving human subjects.

6. The primary purpose of medical research involving human subjects is to understand the causes, development and effects of diseases and improve preventive, diagnostic and therapeutic interventions (methods, procedures and treatments). Even the best proven interventions must be evaluated continually through research for their safety, effectiveness, efficiency, accessibility and quality.

7. Medical research is subject to ethical standards that promote and ensure respect for all human subjects and protect their health and rights.

8. While the primary purpose of medical research is to generate new knowledge, this goal can never take precedence over the rights and interests of individual research subjects.

9. It is the duty of physicians who are involved in medical research to protect the life, health, dignity, integrity, right to self-determination, privacy, and confidentiality of personal information of research subjects. The responsibility for the protection of research subjects must always rest with the physician or other health care professionals and never with the research subjects, even though they have given consent.

10. Physicians must consider the ethical, legal and regulatory norms and standards for research involving human subjects in their own countries as well as applicable international norms and standards. No national or international ethical, legal or regulatory requirement should reduce or eliminate any of the protections for research subjects set forth in this Declaration.

11. Medical research should be conducted in a manner that minimises possible harm to the environment.

12. Medical research involving human subjects must be conducted only by individuals with the appropriate ethics and scientific education, training and qualifications. Research on patients or healthy volunteers requires the supervision of a competent and appropriately qualified physician or other health care professional.

13. Groups that are underrepresented in medical research should be provided appropriate access to participation in research.

14. Physicians who combine medical research with medical care should involve their patients in research only to the extent that this is justified by its potential preventive, diagnostic or therapeutic value and if the physician has good reason to believe that participation in the research study will not adversely affect the health of the patients who serve as research subjects.

15. Appropriate compensation and treatment for subjects who are harmed as a result of participating in research must be ensured.

Risks, Burdens and Benefits

16. In medical practice and in medical research, most interventions involve risks and burdens.

Medical research involving human subjects may only be conducted if the importance of the objective outweighs the risks and burdens to the research subjects.

17. All medical research involving human subjects must be preceded by careful assessment of predictable risks and burdens to the individuals and groups involved in the research in comparison with foreseeable benefits to them and to other individuals or groups affected by the condition under investigation.

Measures to minimise the risks must be implemented. The risks must be continuously monitored, assessed and documented by the researcher.

18. Physicians may not be involved in a research study involving human subjects unless they are confident that the risks have been adequately assessed and can be satisfactorily managed.

When the risks are found to outweigh the potential benefits or when there is conclusive proof of definitive outcomes, physicians must assess whether to continue, modify or immediately stop the study.

Vulnerable Groups and Individuals

19. Some groups and individuals are particularly vulnerable and may have an increased likelihood of being wronged or of incurring additional harm.

All vulnerable groups and individuals should receive specifically considered protection.

20. Medical research with a vulnerable group is only justified if the research is responsive to the health needs or priorities of this group and the research cannot be carried out in a non-vulnerable group. In addition, this group should stand to benefit from the knowledge, practices or interventions that result from the research.

Scientific Requirements and Research Protocols

21. Medical research involving human subjects must conform to generally accepted scientific principles, be based on a thorough knowledge of the scientific literature, other relevant sources of information, and adequate laboratory and, as appropriate, animal experimentation. The welfare of animals used for research must be respected.

22. The design and performance of each research study involving human subjects must be clearly described and justified in a research protocol.

The protocol should contain a statement of the ethical considerations involved and should indicate how the principles in this Declaration have been addressed. The protocol should include information regarding funding, sponsors, institutional affiliations, potential conflicts of interest, incentives for subjects and information regarding provisions for treating and/or compensating subjects who are harmed as a consequence of participation in the research study.

In clinical trials, the protocol must also describe appropriate arrangements for post-trial provisions.

Research Ethics Committees

23. The research protocol must be submitted for consideration, comment, guidance and approval to the concerned research ethics committee before the study begins. This committee must be transparent in its functioning, must be independent of the researcher, the sponsor and any other undue influence and must be duly qualified. It must take into consideration the laws and regulations of the country or countries in which the research is to be performed as well as applicable international norms and standards but these must not be allowed to reduce or eliminate any of the protections for research subjects set forth in this Declaration.

The committee must have the right to monitor ongoing studies. The researcher must provide monitoring information to the committee, especially information about any serious adverse events. No amendment to the protocol may be made without consideration and approval by the committee. After the end of the study, the researchers must submit a final report to the committee containing a summary of the study's findings and conclusions.

Privacy and Confidentiality

24. Every precaution must be taken to protect the privacy of research subjects and the confidentiality of their personal information.

Informed Consent

25. Participation by individuals capable of giving informed consent as subjects in medical research must be voluntary. Although it may be appropriate to consult family members or community leaders, no individual capable of giving informed consent may be enrolled in a research study unless he or she freely agrees.

26. In medical research involving human subjects capable of giving informed consent, each potential subject must be adequately informed of the aims, methods, sources of funding, any possible conflicts of interest, institutional affiliations of the researcher, the anticipated benefits and potential risks of the study and the discomfort it may entail, post-study provisions and any other relevant aspects of the study. The potential subject must be informed of the right to refuse to participate in the study or to withdraw consent to participate at any time without reprisal. Special attention should be given to the specific information needs of individual potential subjects as well as to the methods used to deliver the information.

After ensuring that the potential subject has understood the information, the physician or another appropriately qualified individual must then seek the potential subject's freely-given informed consent, preferably in writing. If the consent cannot be expressed in writing, the non-written consent must be formally documented and witnessed.

All medical research subjects should be given the option of being informed about the general outcome and results of the study.

27. When seeking informed consent for participation in a research study the physician must be particularly cautious if the potential subject is in a dependent relationship with the physician or may consent under duress. In such situations the informed consent must be sought by an appropriately qualified individual who is completely independent of this relationship.

28. For a potential research subject who is incapable of giving informed consent, the physician must seek informed consent from the legally authorised representative. These individuals must not be included in a research study that has no likelihood of benefit for them unless it is intended to promote the health of the group represented by the potential subject, the research cannot instead be performed with persons capable of providing informed consent, and the research entails only minimal risk and minimal burden.

29. When a potential research subject who is deemed incapable of giving informed consent is able to give assent to decisions about participation in research, the physician must seek that assent in addition to the consent of the legally authorised representative. The potential subject's dissent should be respected.

30. Research involving subjects who are physically or mentally incapable of giving consent, for example, unconscious patients, may be done only if the physical or mental condition that prevents giving informed consent is a necessary characteristic of the research group. In such circumstances the physician must seek informed consent from the legally authorised representative. If no such representative is available and if the research cannot be delayed, the study may proceed without informed consent provided that the specific reasons for involving subjects with a condition that renders them unable to give informed consent have been stated in the research protocol and the study has been approved by a research ethics committee. Consent to remain in the research must be obtained as soon as possible from the subject or a legally authorised representative.

31. The physician must fully inform the patient which aspects of their care are related to the research. The refusal of a patient to participate in a study or the patient's decision to withdraw from the study must never adversely affect the patient-physician relationship.

32. For medical research using identifiable human material or data, such as research on material or data contained in biobanks or similar repositories, physicians must seek informed consent for its collection, storage and/or reuse. There may be exceptional situations where consent would be impossible or impracticable to obtain for such research. In such situations the research may be done only after consideration and approval of a research ethics committee.

Use of Placebo

33. The benefits, risks, burdens and effectiveness of a new intervention must be tested against those of the best proven intervention(s), except in the following circumstances:

Where no proven intervention exists, the use of placebo, or no intervention, is acceptable; or

Where for compelling and scientifically sound methodological reasons the use of any intervention less effective than the best proven one, the use of placebo, or no intervention is necessary to determine the efficacy or safety of an intervention

and the patients who receive any intervention less effective than the best proven one, placebo, or no intervention will not be subject to additional risks of serious or irreversible harm as a result of not receiving the best proven intervention.

Extreme care must be taken to avoid abuse of this option.

Post-Trial Provisions

34. In advance of a clinical trial, sponsors, researchers and host country governments should make provisions for post-trial access for all participants who still need an intervention identified as beneficial in the trial. This information must also be disclosed to participants during the informed consent process.

Research Registration and Publication and Dissemination of Results

35. Every research study involving human subjects must be registered in a publicly accessible database before recruitment of the first subject.

36. Researchers, authors, sponsors, editors and publishers all have ethical obligations with regard to the publication and dissemination of the results of research. Researchers have a duty to make publicly available the results of their research on human subjects and are accountable for the completeness and accuracy of their reports. All parties should adhere to accepted guidelines for ethical reporting. Negative and inconclusive as well as positive results must be published or otherwise made publicly available. Sources of funding, institutional affiliations and conflicts of interest must be declared in the publication. Reports of research not in accordance with the principles of this Declaration should not be accepted for publication.

Unproven Interventions in Clinical Practice

37. In the treatment of an individual patient, where proven interventions do not exist or other known interventions have been ineffective, the physician, after seeking expert advice, with informed consent from the patient or a legally authorised representative, may use an unproven intervention if in the physician's judgement it offers hope of saving life, re-establishing health or alleviating suffering. This intervention should subsequently be made the object of research, designed to evaluate its safety and efficacy. In all cases, new information must be recorded and, where appropriate, made publicly available.

Appendix B: Flowchart Showing Actor Relationships

