Meeting Proceedings

OPEN

Regulation of orthopaedic devices: Future implications for research and innovation

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Abstract

The conception-to-market development of orthopaedic devices occurs across the total product life cycle including device design and preclinical testing, clinical investigations to support marketing applications, and monitoring of device performance after market introduction. This process involves industry, regulatory agencies, health care providers, engineers, scientists, and patients. The Food and Drug Administration (FDA) is responsible for regulating medical devices in the United States, and uses a 3-tier classification system based on the level of control necessary to provide reasonable assurance of safety and effectiveness. Classification directs the required regulatory pathway and premarket submission type. Variations in global regulations, particularly between the United States, European Economic Area (EEA), and the United Kingdom (UK), may impact industry response to orthopaedic device development. Changing device innovation and reimbursement models have led to the consolidation of market share among larger companies. Although larger companies are better able to cope with more rigorous regulatory requirements, this leads to decreased competition and increased upward price pressure. To assist with the complex regulatory processes, the FDA offers pre-submission assistance as an opportunity for early collaboration and discussion about the medical device or device-led combination product submissions. Orthopaedic organizations, such as the Orthopaedic Trauma Association (OTA), may assist in postmarket device surveillance through the coordinated development and maintenance of clinical data registries. Such registries can longitudinally follow patients with a specific orthopaedic pathology or device usage, and monitor outcomes towards improvements in next-generation device development. As technology evolves, the nexus of regulation, industry, and patient outcome monitoring will continue to support safe and effective device innovation.

Keywords: data registries, device Innovation, Medical device regulation, orthopaedic industry, regulatory testing

1. Food and drug administration regulation of orthopaedic devices by Dr. Vincent Devlin

1.1. Food and drug administration's center for devices and radiological health

The Food and Drug Administration's (FDA) Center for Devices and Radiological Health (CDRH) is responsible for protecting and promoting the public health. CDRH assures that patients and providers have timely and continued access to safe, effective, and high-quality medical devices and radiation-emitting products. The staff at CDRH utilize a cross-functional, team-based approach across the total product life cycle of medical devices and focus on improving the health and quality of life of patients (Fig. 1).

Abbreviations: AAOS = American Academy of Orthopaedic Surgeons, ACA = Affordable Care Act, ACS = American College of Surgeons, AO = Arbeitsgemeinschaft für Osteosynthesefragen, CDRH = Center for Devices and Radiological Health, CE = Conformité Européene, CMMI = Center for Medicare and Medicaid Innovation, EEA = European Economic Area, EMR = Electronic Medical Record, FDA = Food and Drug Administration, HRRP = Hospital Readmission Reduction Program, IDE = Investigational Device Exemption, IFU = Instructions For Use, IPAB = Independent Payment Advisory Board, JBJS = Journal of Bone & Joint Surgery (JBJS), JOT = Journal of Orthopaedic Trauma, KOL = Key Opinion Leader, MDR = Medical Device Regulations, MIPS = Merit-Based Incentive Payment System, MOPS = Missouri Osteochondral Preservation System, NEST = National Evaluation System for health Technology, OTA = Orthopaedic Trauma Association, QI = Quality Improvement, SIR = Submission Issue Request, UK = United Kingdom, US = United States.

Source of funding: Nil.

Potential Conflicts of Interest: Drs. Harris, Poggie, Sanders, and Morshed are members of the Orthopaedic Trauma Association. Dr. Devlin is a Chief Medical Officer with the United States Food and Drug Administration. Dr. Poggie has financial relationships with Bodycad Inc., Acuitive Technologies Inc., Biorez Inc., Corin Ltd., NextStep Arthropedix, Optimotion Implants, and Cerapedics. Otherwise, the authors have nothing to disclose.

The study was deemed exempt from Institutional Review Board and Animal Use Committee Review.

This work received no funding. Dr. Devlin and the FDA only assume responsibility for information provided within his section of the manuscript.

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OTA (2021) e101

Received: 26 September 2020 / Received in final form: 9 November 2020 / Accepted: 13 December 2020

Published online 15 April 2021

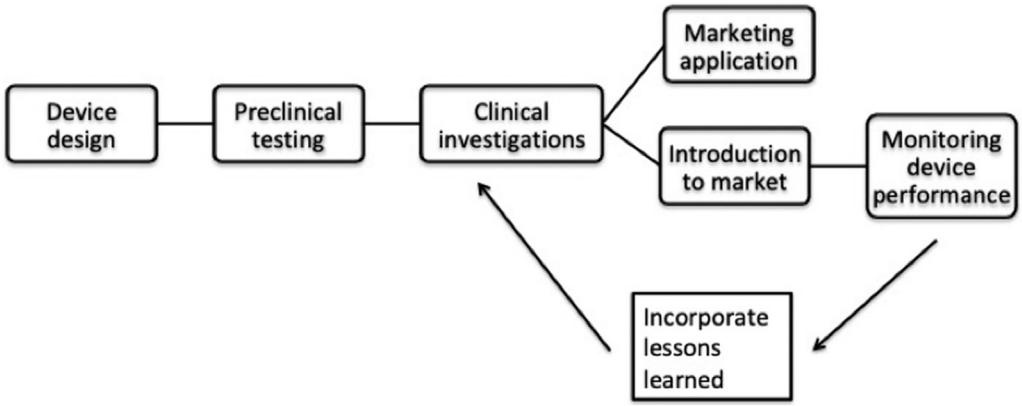

Figure 1. The total product lifecycle for medical devices. The total product life cycle includes device design, preclinical testing, and clinical investigations to support a marketing application. Device performance monitoring continues following market introduction. Lessons learned from device development and widespread device use are incorporated into the development of the next generation of devices.

The types of data and testing required to market a medical device in the United States are determined by the device classification, mechanisms of operation, technological characteristics, and labeling. Although the FDA regulates the interstate commerce of medical device products in the United States and monitors the safety of regulated medical devices, it does not have the authority to regulate an individual clinician's practice.[1] However, when clinicians use a device that is not approved for a specific indication in the context of an investigation, this is different from the practice of medicine and is considered investigational use. For significant risk devices, FDA approval of an investigational device exemption,[2] or IDE, is needed to conduct these types of clinical research studies (Table 1). Patients with immediately life-threatening conditions or serious diseases or conditions can access unapproved investigational medical devices outside of clinical trials when no comparable or satisfactory therapy options are available through FDA's Expanded Access Program[3] based on specific criteria (Table 2).

CDRH has made it a strategic priority to strengthen the clinical trial enterprise in the United States. CDRH is highly interactive with stakeholders during review of their IDE submissions, encourages the use of efficient trial designs, and requires the minimum necessary information to adequately address regulatory questions. Examples of special programs (Table 3) include the Early Feasibility Study Program,[4] a voluntary program designed to facilitate the conduct of early feasibility IDE studies in the United States, and the Breakthrough Devices Program,[5] which is directed toward sponsors of medical devices and device-led combination products that provide for more effective treatment or diagnosis of life-threatening or irreversibly debilitating diseases or conditions. As of September 2019, the FDA issued a draft guidance for comments introducing a new voluntary program, the Safer Technologies Program, for medical devices and device-led combination products that are reasonably expected to significantly improve the safety of currently available treatments or diagnostics that target an underlying disease or condition less serious than those eligible for the Breakthrough Devices Program.[6] These efforts have contributed to a notable increase in the number of novel devices reaching the US market over the past decade, while maintaining high standards for device safety and human subject protections.

1.2. Real-world data and medical device lifecycle

In addition to data from traditional nonclinical and clinical studies, CDRH recognizes that a wealth of real-world data

Table 1

Types of investigational device exemption studies.

Early feasibility study	A limited clinical investigation of a small number of subjects for a device early in development, typically before the device design has been finalized
Traditional feasibility study	A clinical investigation used to capture preliminary safety and effectiveness information, usually in a small number of subjects, on a near-final or final device design and to plan an appropriate pivotal study
Pivotal study	A clinical investigation designed to collect definitive evidence of the safety and effectiveness of a device for a specified intended use, typically in a statistically justified number of subjects

Table 2

Types of expanded access for medical devices.

Emergency use	Use of an investigational device when an individual patient is in a life-threatening situation and needs immediate treatment
Treatment use	Use of an investigational device to treat or diagnose a group of patients with a serious or immediately life-threatening condition when the device is also being studied for the same use under an approved investigational device exemption
Compassionate use	Use of an investigational device to treat or diagnose an individual patient or a small group of patients with a serious disease or condition when there are no available alternative options

Table 3

Special programs to promote medical device innovation at Center for Devices and Radiological Health.

Early Feasibility Study Program	Facilitates conduct of early feasibility studies in the United States
Breakthrough Devices Program[a]	Eligible devices required to meet two criteria:
	Provide for more effective treatment or diagnosis of life-threatening or irreversibly debilitating disease or condition
	The device also meets at least 1 of the following:
	Represent breakthrough technology
	No approved or cleared alternatives exist
	Offers significant advantages over existing approved or cleared alternatives
	Device availability is in the best interest of patients

[a] For sponsors of devices subject to premarket approval applications (PMAs), premarket notification (510(k)) or requests for De Novo designation.

regarding medical devices exists and are routinely collected in the course of management and treatment of patients.[7] Real-world data include data derived from electronic health records, claims and billing records, product and disease registries, and personal devices and health applications. In some circumstances, this real-world data may be of sufficient quality to constitute real-world evidence and can be used by CDRH to inform understanding of the benefit-risk profile of medical devices at various points in their life cycle. CDRH is leveraging experience with real-world evidence through collaboration with medical device stakeholders to build the National Evaluation System for health Technology (NEST).[8] NEST joins together stakeholders from across the medical device ecosystem to generate evidence at each stage of the medical device life cycle. This real-world evidence may then be leveraged through advanced analytics to create data tailored to specific medical devices. Another real-world evidence effort that the FDA and external stakeholders are advancing the development of is Coordinated Registry Networks in diverse areas, including orthopedic surgery.

1.3. Patient engagement

At the core of the development process for any medical device is patient engagement. CDRH's Patient Science and Engagement Program[9] facilitates interactions between staff and individual patients and patient groups to enhance understanding of patients' perspectives and integrate patient input into regulatory decision-making. This has led to an increase in the use of patient-reported outcome measures and patient preference information to support regulatory decisions towards advancing the development of various programs that allow staff and patients to work collaboratively.

1.4. Conclusion

As technology continues to advance, so will the medical devices used by patients. By understanding and helping to shape the science that supports these advances, the FDA will continue to spur medical device innovation in a safe and effective manner.

2. Regulatory trends in clinical testing: implications in Europe and North America by Dr. Robert Poggie

2.1. Financial investment and timeline of clinical development

The process of bringing a medical device from conception to market can be costly in terms of both time and money, depending on the risk level of the device. For lower risk devices, total costs can range from the $10,000's to $100,000 s, whereas full product launches from large companies with greater numbers of component costs and consultation fees may be more expensive, particularly for higher risk devices. A 2010 survey of 200 medical technology companies placed the average total cost for moderate-risk devices at $31 million ranging to over $94 million for higher risk products, of which over 75% was spent on regulatory activities.[10] Broadly, the multi-stage requirements of regulatory testing follow a "rule of 10's," with basic laboratory testing starting in the $10,000 range, increasing to the $100,000 range for functional animal modeling, and ranging to over $1,000,000 for clinical trials. Clinical trial costs vary dramatically depending on number of enrolled patients and required follow-up time.[11] These regulatory testing costs are tolerated under the expectation of recouping losses through profit when devices come to market. However, time to market may vary from weeks, to months, to years, thereby impacting sales and return on laboratory investment.[11] This process introduces competing interests often within the same broader context of national/provincial government: payers wish to decrease time to market, whereas regulators must ensure that time to market is sufficient to ensure product safety.

2.2. Regulatory classification and implications

In the United States, the FDA regulates implants and devices. In order to standardize required laboratory testing before products come to market, the FDA divides devices in 3 regulatory classes[12] based on risk, and in turn the level of control necessary to ensure effectiveness and device safety.[13] Class I is the least regulated, and Class III the most regulated.[13,14] For example, a non-powered goniometer, a purely external device, is listed as Class I, whereas an arthroscope, an endoscope device for visualization of an interior joint, is Class II.[1] Implantable devices may be Class II, such as an intramedullary nail, or Class III if considered a greater risk, such as an intervertebral disc prosthesis.[1,15] Class I and II rarely require human clinical data, instead relying on well-defined basic science testing methods and predictable regulatory reviews.[14] Therefore, Class I and Class II devices typically take under a year for required testing and modification, and are relatively low-cost through the FDA 510K pathway.[14] Conversely, Class III devices generally require clinical testing, are therefore more expensive, and may take years to reach market with uncertain return on investment. As such, Class I and II devices have historically dominated the market relative to higher risk Class III devices.

Although currently under revision, the European regulatory system also relies on a tiered device class designation system, in addition to the Conformité Européene (CE) mark. The CE mark signifies that a product meets all legal safety, health, and

environmental requirements and may be distributed and marketed within the European Economic Area (EEA). Comparable clinical testing outside the US (e.g., Canada, Australia, Western Europe) can provide dramatic cost savings of 30% to 50% or more, depending on the US sites chosen for testing, which has shifted global market shares of clinical testing outside the United States.[11] However, changing European device regulations (MDRs) are realigning back toward the United States for the global market share of regulatory testing for Class II and III devices. As of April 2017, new European regulations require devices to have more stringent clinical evidence requirements to obtain and maintain the CE mark than before, especially for Class II devices.[16] Under the new MDRs, Class II and Class III products are also subject to rigorous postmarket surveillance requirements. This results in higher cost and time barriers to market for new implants, even if implants have only minor differences in design and technology from available implants.

The delay in the marketing of similar implants due to increased regulations in Europe has had several important downstream effects. These regulations have significantly increased the cost of maintaining product lines, which has led to the disappearance of smaller companies with low-volume products, although this consolidation trend has been in progress for some time. Between 1999 to 2015, large company acquisitions of smaller companies led to the consolidation of market share in the top 5 orthopaedic device companies from 52.8% to 62.2% overall.[17] Larger, global companies that can contract out MDR compliance are better able to withstand more rigorous regulations. However, fewer products and company options have led to reduced competition and increased upward price pressure.[17]

2.3. Food and drug administration regulations and the Q-submission program

One US solution for decreasing unnecessary testing costs and time to market is the FDA's Q-Submission Program.[18] The Q-Submission Program is a voluntary program that provides an opportunity to gain formal FDA feedback regarding components of a potential or planned medical device submission.[18] A presubmission is often requested when a premarket submission requires tests that are costly and time-consuming, such as animal modeling or clinical trials, and where there are no detailed FDA guidance documents.[18] In this situation, the company requesting the presubmission defines the product, instructions for use (IFU), classification, and proposed test plans for which FDA feedback is requested.[18] The FDA then reviews and provides feedback in writing, teleconference, face-to-face meetings, or a combination thereof. This assistance in navigating device regulation may help companies comply with regulatory requirements, increasing the likelihood of FDA approval without revision testing.[18] Interactions with the FDA once a submission has already occurred would fall under a Submission Issue Request (SIR), a separate mechanism to request FDA feedback on proposed approaches for addressing issues conveyed in a marketing submission hold letter or other types of hold letter.[18] The Q-Submission Program may also be helpful globally, as most regulators follow US guidance for laboratory performance data.

2.4. Conclusion

The sophistication and number of preclinical tests is increasing as the industry matures and technology and accessibility of information enable both regulators and device engineers to develop novel devices. The FDA has an extensive digital infrastructure for managing device regulations, which is useful for data-mining regulatory testing plans and finding guidance for country-based applicability. If the proposed testing plan is complex or costly, an FDA presubmission is highly recommended. New MDRs in Europe are increasing time-to-market for novel products, particularly for Class II devices. These more rigorous regulations are likely to increase device costs and may decrease the European market share of clinical device regulatory testing.

3. Implant design and research: what does industry value? by Dr. Roy Sanders

3.1. History of orthopaedic device innovation

Before the 1980s, orthopaedic device innovation centered around small manufacturers of basic equipment such as K-nails, hip screws, and external fixators. Following the manufacture of orthopaedic devices by Synthes in the 1980s, Synthes emerged as a dominant player in the orthopaedic device market into the early 2000s, when other companies were finally able to bring competing products to market. This period, between 1990 and 2010, became known as the "golden age" of device innovation. Orthopaedic organizations such as OTA and the AO served to develop key opinion leaders (KOL), connecting the industry with individual surgeons who provided new designs and innovation based on absolute user needs.

3.2. Surgeon reimbursements and orthopaedic market maturation

The 2010 introduction of the Affordable Care Act (ACA) contained several provisions with direct effects on Medicare payments for orthopaedic surgery, particularly the Independent Payment Advisory Board (IPAB), the Hospital Readmission Reduction Program (HRRP), and the Center for Medicare and Medicaid Innovation (CMMI).[19] The IPAB is tasked with curbing Medicare expenditures, HRRP targets reduction in patient readmission within 30 days of hospital discharge, and CMMI programs involve payment "bundling" such that payments for hospitals and all hospital physicians would be "bundled" together.[19] Orthopaedic surgery, particularly arthroplasty, became an early target of bundled payments.[19] Additionally, financial payments by orthopaedic device makers to orthopaedic surgeons became a target of healthcare reform, with a 2007 Department of Justice settlement resulting in a 42% drop in the number of industry payments below $25,000 to individual orthopaedic surgeons.[20] Although there are a variety of ethical considerations surrounding the relationship between orthopaedic surgeons and the device manufacturing industry,[21] the decline in such payments decreased the proportion of orthopaedic surgeons who consulted with device manufacturers.[20] Without the same degree of input from practicing orthopaedic surgeons, technological change dropped precipitously, limiting innovation. This then started the shift to acquisition rather than in-house development of new technology.[20]

3.3. Small-scale device research and development in modern markets

The current strategy of the orthopaedic device industry has now become one of merger and consolidation[17] whereby market

shares are combined amongst a few key market players to form an oligopoly. It is less expensive for companies to buy technology than to develop products in-house. As such, large companies are interested in (1) having KOLs use orthopaedic devices in their practice for post-market surveillance and as marketing tools, (2) emerging technologies published in high impact journals, and (3) small companies with FDA approved products that can be acquired and more quickly brought to market.

If an individual surgeon wishes to directly enter the orthopaedic device manufacturing market, product development begins with (1) a search to ensure no patents exist, (2) financing the project, which may be self-funded, obtained from family and friends, or come from small engineering firms, and (3) an engineer experienced in implant design. Once these are obtained, the next 3 months are taken up with design files, prototypes, proof of concept, and patent filing. The following 3 years will include the FDA's 510K application (see Section 2), manufacturing costs, final lab testing, and sterilization, with estimated total costs between $500,000 and $1,000,000, though notably still only a fraction of the full $31 million cited by large companies taking devices from concept to final marketing.[10] Once developed, the device can then be (1) sold to a large company, who would then take on marketing responsibilities, or (2) sold via independent distributors. If sold to a company, standard pricing models include 50% payment upfront with 50% paid as a royalty stream based on device sales. As with any market, device sales can be unpredictable, and recouping product expenditures uncertain.

3.4. Conclusion

The orthopaedic device market is in flux, with consolidation of marketing power in a few top companies who buy, rather than create technology, whereas device innovation is left for smaller companies with an uncertain return on investment.

4. Registries and databases: data assets and the promise of orthopaedic trauma registries by Dr. Mitchel Harris

4.1. Clinical data registry and academic database

A clinical data registry is defined as any record using observational study methods to collect patient health information over variable time periods.[22] Such information may include (1) specific disease conditions or exposures, (2) procedures, or (3) device performance tracking. This data may be utilized to illustrate available treatments, treatment outcomes, or treatment response variability based upon differing patient characteristics. Academic databases are similar, but instead follow a carefully selected patient cohort with a specific disease or condition (Table 4). Although registries currently diverge from academic databases in terms of "purpose" and "type" of collected data,[22,23] as digital technologies that support registries improve, a convergence of their respective scope of process and outcome metrics is likely to occur.

Clinical data registries assist device regulatory compliance as they allow for independent postmarket surveillance, facilitating the process of regulatory scrutiny, especially of Class II devices. Registries first enable internal tracking and monitoring of patient outcomes with longitudinal data. When combined, registries may be applied toward initiatives such as payer incentivized quality improvement (QI) projects, and afford access to on-demand, practice-specific quality reports and dashboards to compare local, regional, and national best-practice guidelines. Registry data may additionally be utilized in clinical practice databases such as the Joint Commission Advanced Certification, the Merit-Based Incentive Payment System (MIPS), and the Missouri Osteochondral Preservation System (MOPS), among others.

4.2. Obstacles to registry development and sustainability

There are several important obstacles to registry development and sustainability: cost, interoperability, and vendor collaboration.[23,24] Operating registries and connecting them directly with source data systems, such as electronic medical records (EMR), requires a significant investment in both technology and funding. Across the United States, funding sources to cover these costs include self-funding, funding from specialty societies, registry participation fees, private, industry, or federal grants, or fees charged for data use.[24] The second obstacle, interoperability, is the ability for different computer systems ("structural") or software ("semantic") to readily "communicate" and facilitate information exchange. For example, successful interoperability may enable linking databases across multiple sites, structural interoperability, or between different systems of electronic medical records, semantic interoperability. Ultimately, improved interoperability will result in significantly reduced data acquisition costs as well as better data quality.

The development of any registry requires a determination of data rights. Single-site departmental and hospital-based registries have primary data ownership. National and society-based registries own the aggregate, de-identified data collected from all participating sites, including data collected as part of "add-on" research projects and other efforts utilizing the national registry or Society platform and data storage. Notably, individual contributing centers may opt out of center comparisons, or negotiate rights to have a voice in decisions about aggregate studies.

4.3. Registry development in practice

Efforts to realize the promise of registries in orthopaedic surgery are currently underway at the level of the American Academy of Orthopaedic Surgeons (AAOS), Orthopaedic Trauma Association (OTA), and Arbeitsgemeinschaft für Osteosynthesefragen (AO). In 2017, the AAOS approved a multi-year investment in

Table 4

Essential differences between a clinical data registry and academic database.

Dataset	Collected data	Database purpose
Clinical registry	*Limited* data on: Specific procedure Any procedure for a specific condition	*Quality:* monitor treatment activity and performance
Academic database	*Extensive* data on: Cohort of carefully selected subset of patients	*Knowledge generation:* inform standard of care for patients with a specific condition

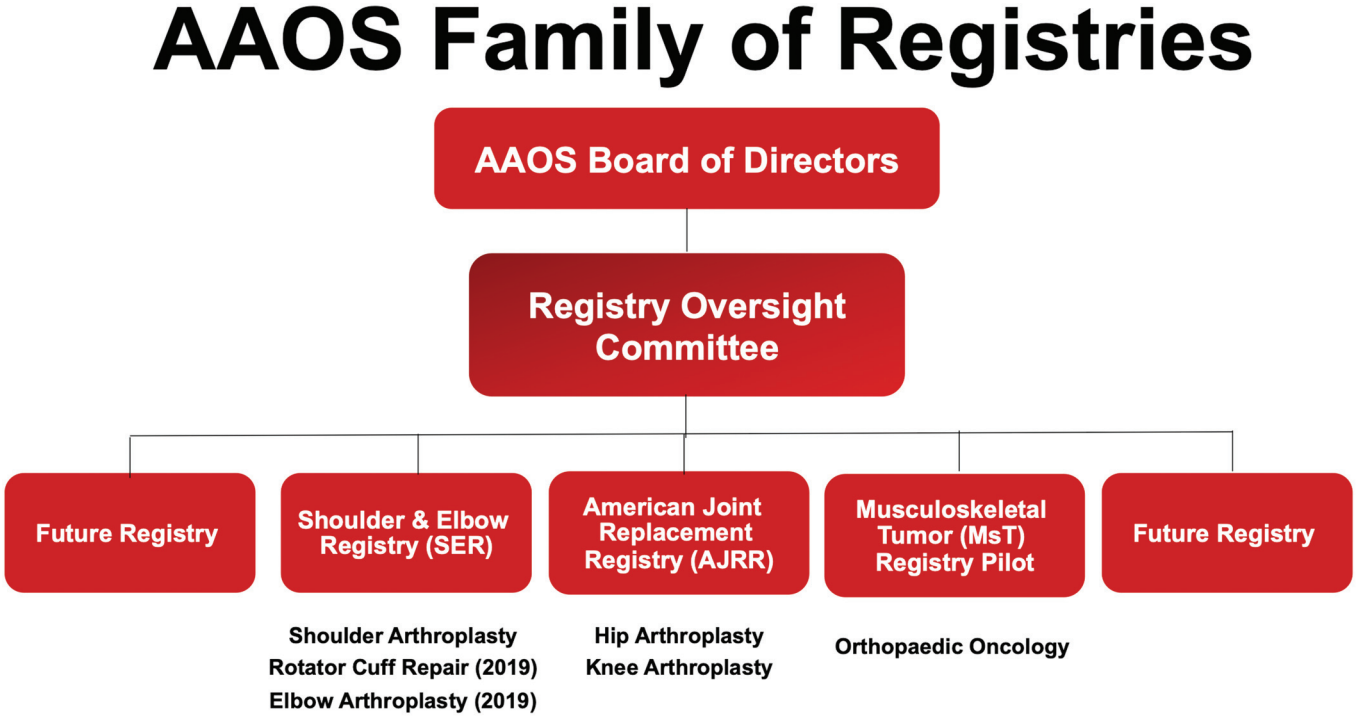

Figure 2. American Academy of Orthopaedic Surgeons (AAOS) registry flowchart. The current family of American Academy of Orthopaedic Surgeons (AAOS) registries and hierarchy of oversight. Current registries include the Shoulder & Elbow Registry (SER), American Joint Replacement Registry (AJRR), and Musculoskeletal Tumor (MsT) Registry Pilot.

registry development with the explicit goal of bridging the gap between science and clinical practice.[25] In pursuit of this goal, the AAOS developed a Registry Oversight Committee (Fig. 2), which oversees current AAOS registries, and collaborates with internal and external organizations towards future registry development.[25] Within this model, registries serve as the data-source to promote continuous quality improvement that translates science into clinical practice. Specifically, registries (1) provide data to inform AAOS guidelines and performance measures, (2) provide feedback to individual providers to continuously improve their practice, (3) allow AAOS to define quality, and (4) reduce the reporting burdens on physicians.[25]

In 2019, AAOS and OTA initiated the development of a collaborative registry with the goals of (1) identifying opportunities to improve care for complex orthopaedic trauma conditions, (2) providing an infrastructure for members to participate in data gathering, (3) providing OTA members with de-identified data for clinical research purposes, and (4) exploring collaborative opportunities with industry partners to accumulate and evaluate fracture care and implant performance data. In March of 2020, the OTA Registry Project Team described a 3-pronged approach of registry development, thereby minimizing cost, dispersing risk, taking advantage of partner expertise and experience, and setting a platform for future expansion into research, MIPS, MOPS, QI, and others.

Prong 1 is developing a partnership with the American College of Surgeons (ACS) to use process or inpatient outcome metrics, such as the incidence of tibia fractures and compartment release, time to coverage of AO Classification[26] IIIB tibia fractures, or incidence of inpatient infection of AO Classification IIIB tibia fractures. These metrics will further be used for ACS accreditation. Prong 2 describes a partnership with AAOS for a fracture/trauma registry run by a steering committee of trauma surgeons. This registry component will emphasize hip fractures, proximal humerus fractures, and ankle fractures. Prong 3 describes a partnership with AO to make a private data management system available for 2 to 3 orthopaedic trauma-specific injury registries. Under this model, each center would own its own data, but have the option for blinded data to be pooled toward high-powered data analysis. The registry would utilize the industry data management backbone of previously developed data fields for rapid implementation, and each participating center would be able to expand the umbrella data collection tool to address site-specific needs. Presently, these OTA/AAOS, OTA/ACS, and OTA/AO registry projects remain aspirational as efforts continue to reconcile feasibility and expense.

4.4. Conclusion

Registries provide timely, actionable, and specific feedback to participating clinicians and hospital departments. The remaining obstacles to registry development include improving interoperability, finding sustainable funding sources, and negotiating data ownership. Despite these challenges, the information gathered on relative quality of performance, both locally and nationally, may inform strategies for future improvement.

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