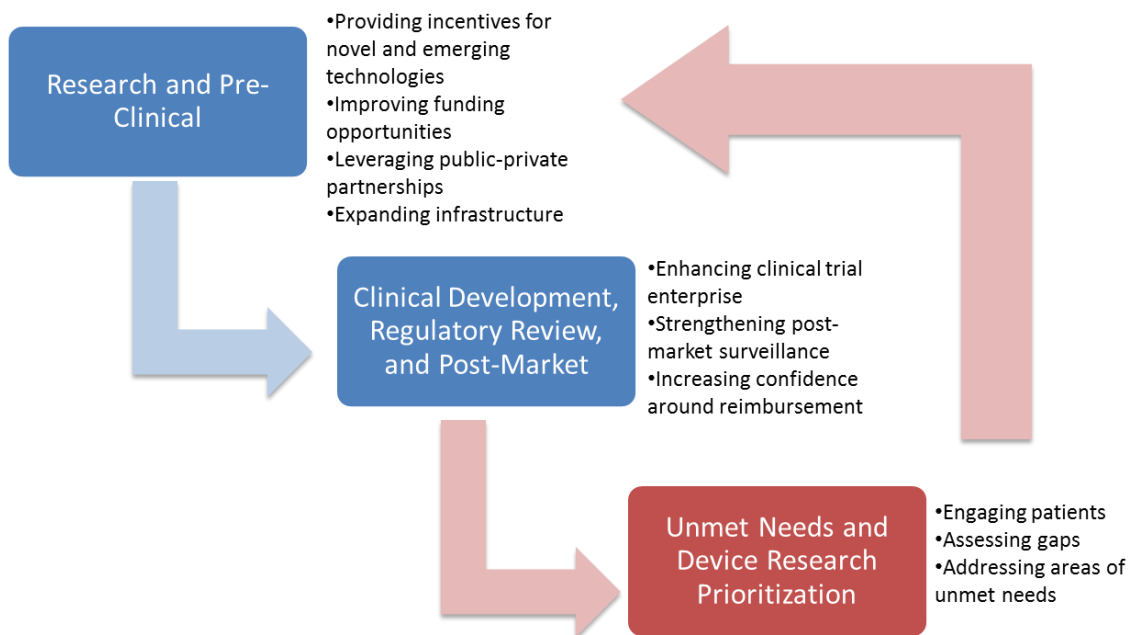


Biomedical Innovation: Identifying Challenges and Prioritizing Needs in Medical Device Research and Development

Introduction

Medical device innovation in the United States is entering an era of unprecedented change. Rapidly evolving technology, emerging markets, an increasingly globalized development process, and evolving health policy reforms are presenting device manufacturers with unprecedented opportunities for valuable innovation, but are also creating significant challenges to the current development paradigm. In order to translate novel and emerging technologies into safe and effective devices that can benefit patients, it is paramount that the United States sustains entrepreneurship and maintains an environment conducive for innovation. Many ideas have been proposed to help achieve these goals, and public and private initiatives related to medical device research and development are underway. Recognizing the need for manufacturers, regulators, payers, investors, patients, and other stakeholders with important roles in the medical device ecosystem to engage in a thoughtful discussion on these issues, the Engelberg Center for Health Care Reform, with the generous support and collaboration of the National Institutes of Health (NIH), is convening a full day workshop focused on improving medical device innovation. The resultant policy initiatives, paired with mechanisms to support more effective stakeholder collaboration, should improve incentives and support entrepreneurs, streamline the clinical development and regulatory process for safe and effective treatments, and improve patient access to innovative high quality devices. The resulting device development ecosystem (Figure 1) will be one that moves with both speed and assurance to provide novel medical devices to those in need.

Figure 1: The Medical Device Innovation Ecosystem



Workshop Background and Objectives

The Brookings workshop will include discussion of issues across a spectrum of devices (e.g., implants, radiological imaging, *in vitro* diagnostics), at different stages of developmental pipeline, and targeting varied clinical impacts (e.g., unmet need, quality of life). Over the course of the day, participants will address the challenges the medical device industry is facing in developing novel technologies that meet the needs of patients. Achieving those aims effectively will require an across-the-board examination of the key challenges faced by medical device manufacturers and innovators throughout the device development pipeline. All stages of development, including early research and proof-of-concept phases, non-clinical testing, clinical testing for regulatory approval, evidence generation for reimbursement, and performance and safety tracking during clinical use will need to be explored comprehensively to identify areas where policy improvements can have the greatest impact. This workshop will serve as a forum to discuss actionable strategies to enable government, industry groups, public-private partnerships, and other actors to create an environment that is conducive to innovation and entrepreneurship, while ensuring that incentives exist to move innovation into otherwise unaddressed disease areas.

The workshop will feature discussion-oriented sessions, beginning with a set of perspectives on the current state of medical device innovation and where the grand challenges lie. This framing conversation will form the foundation for three interactive sessions in which a few lead discussants will begin with brief remarks, followed by an open discussion among all participants in the room.

Special emphasis will be given to the following challenge areas in an effort to identify potential strategies or policy initiatives that may have the greatest impact:

- Incentives for investment in research and development for novel devices;
- Incentives for investment in small markets and rare diseases;
- Compelling business models for startups, small companies, and academia for product development;
- Adequate and efficient infrastructure to support translational science, pre-clinical, and clinical testing;
- Transparent, clear regulatory pathways for new and emerging technologies;
- Efficient mechanisms and infrastructure to support evidence generation needed for approval and reimbursement decisions;
- Efficient mechanisms and infrastructure to support real-world effectiveness and post-market safety evidence generation;
- Clear formal and standardized ways for patients to provide input into needs assessment, benefit-risk calculations, and clinical practice.

Research and Pre-Clinical Development Challenges in the Current Environment

Within the research and pre-clinical phases of development, opportunities exist to shore up and improve the support given to early entrepreneurs, whether it is through technical advice and toolkits or through financial mechanisms. Enhanced funding opportunities, for example, provide the necessary backbone for building out a new technology, as a lack of funding opportunities can chill otherwise promising innovation. This is especially true where exploratory technologies require strong seed funding to establish proof-of-concept. Along with the Small Business Innovation Research (SBIR), Small Business Technology Transfer (STTR), and other grant mechanisms, venture capital has been a primary funder of

such innovation for smaller medical device companies and other innovation hubs, particularly in the initial stages of medical device development. However, in recent years venture capital support has declined as a result of a variety of factors, including escalating time, cost and uncertainty associated with the development and regulatory review process, as well as with reimbursement status.¹ The decline in venture capital funding has been compounded by an overall shift away from early-stage funding and towards products in later-stages of development that have demonstrable potential.² This funding environment has eroded opportunities for medical device start-ups and necessitated new funding mechanisms, such as crowd funding, that have emerged as a means to provide early-stage capital, primarily for proof-of-concept.^{3,4} Examining new paradigms for funding opportunities will be key to ensuring a robust medical device innovation enterprise.

Leveraging public-private partnerships (PPPs) is another important area of opportunity to consider in the research and pre-clinical phases. Serving as a forum for collaboration, PPPs can be uniquely positioned to engage stakeholders across the medical device lifecycle in conversation. However examples of these partnerships are rare in medical device development. The Medical Device Innovation Consortium (MDIC) is one such cross-disciplinary effort working to examine a broad array of issues, such as improving clinical trials, enhancing confidence via computer models, providing “incubator” facilities for novel devices, and bringing the patient voice to benefit-risk assessments.⁵ Early collaboration across stakeholders groups, particularly in earlier stages of the medical device lifecycle, represents a new paradigm for aligning goals and providing a strong push for innovation.

In the workshop’s first session, participants will explore key challenges and strategies related to these and other themes in the research and pre-clinical stages of the medical device product pipeline. Topics of interest for discussion include the following:

- What factors dominate investment in medical device research? How can we incentivize entrepreneurs?
- How can the government and the private sector be influential in aligning economic needs of medical device innovators? How can we leverage and harmonize these efforts to build a medical device ecosystem that supports device innovators?
- Aside from economic factors, how can government, non-government, and academic efforts promote device innovation? How can we create an environment conducive for innovation? What other facilities and resources are needed for innovation? Are they device or technology specific?
- How do we build public-private partnerships and collaborative frameworks to promote device innovation?

¹ National Venture Capital Association (NVCA) and the Medical Innovation and Competitiveness (MedIC) Coalition. Patient Capital 3.0: Confronting the Crisis and Achieving the Promise of Venture-Backed Medical Innovation. 2013. Available at:http://www.nvca.org/index.php?option=com_content&view=article&id=268&Itemid=103

² Pulse of the industry:medical technology report 2013. Redefining innovation. For more information see: <http://www.ey.com/US/en/Industries/Life-Sciences/Pulse-of-the-industry---medical-technology-report-2013>

³ Hughes, Virginia. "Strapped for funding, medical researchers pitch to the crowd." *Nature medicine* 18, no. 9 (2012): 1307-1307.

⁴ Torr-Brown, Sheryl. "Crowdsourcing for Science and Medicine: Progress and Challenges." *The Journal of OncoPathology* 1, no. 2 (2013): 75-81.

⁵ Medical Device Innovation Consortium Works to Reform Approval Process. For more information see: <http://www.mddionline.com/article/medical-device-innovation-consortium-works-reform-approval-process>

- What business models currently support medical device innovation? What are the key challenges that exist in this area? Are there any new business models that can be leveraged to promote device innovation?
- What is the role of Small Business Innovation Research (SBIR) grants, Small Business Technology Transfer (STTR) Program, and similar initiatives in medical device innovation?
- What financially supportive roles should government agencies play to meet innovators' needs?

Clinical Development, Regulatory Review, and Reimbursement

The clinical development and regulatory approval process represents a markedly different set of challenges from the investment and basic research considerations outlined above. The amount of seed or startup capital solicited during proof-of-concept phases must be multiplied many times over to support clinical study. Timelines expand as developers work to fulfill trial requirements and recruit patients into testing. Early stage development targets give way to more rigorous evidentiary standards necessary for regulatory review and coverage decisions. In short, the scope of issues facing a developer widens considerably, which can be especially daunting for small device firms or emerging technology developers unfamiliar with these processes. Adequately equipping these innovators to successfully navigate the path to market entry will require a constellation of policy initiatives and partnerships aimed at creating a nimble, efficient, and collaborative evidence generation infrastructure.

During clinical development, streamlining trials to accurately but efficiently accrue the necessary evidence on the safety and effectiveness of devices will be fundamental to safeguarding innovation and investment. One path to achieving this could be to involve regulators, payers, patients, and specialty providers much earlier in the clinical development process to both understand the evidentiary requirements of the various decision-makers involved in determining patient access and to better align perspectives on the potential value that the technology could introduce to the health care system. For example, while it is unlikely that a single trial could provide the necessary evidence for regulatory approval and health plan coverage, early conversations with regulators and payers could inform novel and flexible trial designs that provide more efficient patient enrollment and seamless execution of studies that address regulatory requirements and development of evidence to support coverage decisions.

As a device enters regulatory phases, opportunities also exist to improve translation of novel technologies from development to use. For example, FDA's Center for Devices and Radiological Health (CDRH) has taken active measures to expedite the regulatory process in an effort to ensure earlier access to novel devices for patients with unmet need. The Agency recently issued a guidance on investigational device exemptions for early feasibility medical device clinical studies⁶ that was well received by industry. This guidance outlined changes that require: less nonclinical data than traditional feasibility or pivotal studies, identifying data needed to support early feasibility studies according to comprehensive device evaluation strategies, and allowance for timelier device and clinical protocol changes during these studies. Another guidance issued recently titled, "Factors to Consider when Making Benefit-Risk Determinations in Medical Device Premarket Approval and De Novo Classifications,"⁷ provides greater clarity on FDA's decision making process. Additionally, the agency has

⁶ US Food and Drug Administration, Guidance on Investigational Device Exemptions (IDEs) for Early Feasibility Medical Device Clinical Studies, Including Certain First in Human (FIH) Studies. 2013 Oct 1.

⁷ US Food and Drug Administration, Guidance on Factors to Consider When Making Benefit-Risk Determinations in Medical Device Premarket Approval and De Novo Classifications. 2012 28 Mar.

identified strengthening the clinical trials enterprise and striking the right balance between pre-market and post-market data collection as two of CDRH's strategic priorities for 2014-15.

Creating clinical development and regulatory mechanisms to streamline evidence collection and FDA approval does not come without potential downstream challenges, however. As developers and regulators search for ways to strike a balance between acceptable pre- and post-market levels of evidence generation, payer groups may find themselves at the point of product approval with smaller pools of clinical data to support coverage. These issues, both the appropriate balance of regulatory requirements pre- and post-market and the resultant challenges facing payers, were highlighted during a recent forum on "Patient Access to High-Risk Devices for Unmet Medical Needs" held by the PEW Charitable Trust.⁸ Many participants agreed that while moving some of the evidence generation to the post-market arena for certain devices (e.g., those in therapeutic areas with unmet needs or small markets) may expedite FDA approval, existing evidence for these devices invariably fail to address questions needed for reimbursement decisions. As mentioned above, there may well exist collaborative development plans where payer evidentiary needs could adequately be addressed in a swift clinical trials process, but for many more development opportunities, device firms, regulators, and payers will need to explore new ways of interacting and allocating evidence generation activities. Thus payer groups may require a significant paradigm shift in how they view products clearing the pipeline's regulatory hurdle via expedited pathways.

A number of tools exist in the post-market space that could be utilized to ameliorate some of the tension between expedited clinical development and payer evidentiary requirements. As health information technology adoption grows, for instance, so does the infrastructure to support more efficient post-market evidence generation on the safety and real-world effectiveness of medical devices. As registries are expanded with more electronic health data collected through routine care and electronic data systems are enriched with unique device identifiers (UDIs), a more robust national post-market surveillance system for medical devices is also feasible. With these systems in place, along with the proper methodology and infrastructure to support leveraging electronic health care data sources (e.g., registry data, claims, EHR data), stakeholders could begin to harness multiple strategies in rethinking the current approval and coverage paradigms. For example, policy initiatives like Medicare's Coverage with Evidence Development (CED), which provides Medicare beneficiaries access to medical technologies contingent on continued collection of clinical evidence on their use in the Medicare population, could make impactful use of such a national post-market infrastructure. One could envision other collaborative agreements that provide coverage for novel technologies while also actively engaging in evidence generation through an enhanced post-market surveillance system. This could also be true at FDA, where regulators could utilize the same wealth of post-market data streams to confidently identify when evidence on the benefits of a specific device's use is substantial enough to warrant an indication expansion without the added burden of expensive and lengthy additional trials. Recent success in this approach can be seen in the expansion of indications for use of transcatheter valve therapy (TVT) based on data from the Society of Thoracic Surgeons (STS) and American College of Cardiology (ACC) TVT Registry.⁹

⁸ Medical Device Innovation: Patient Access to High-Risk Devices for Unmet Medical Needs
<http://www.pewhealth.org/other-resource/medical-device-innovation-patient-access-to-high-risk-devices-for-unmet-medical-needs-85899536274>

The workshop's second session will tackle many of these issues related to clinical development, regulatory approval, and reimbursement decisions for novel medical devices. Potential topics for discussion include the following:

- What funding mechanisms or business models are available for innovators to push from proof of concept stage to clinical development?
- Are there examples from other industries that can be used to drive innovation at this stage?
- How can innovators access infrastructure such as clinical trial sites, manufacturing, and other resources? How can this infrastructure for clinical trials be expanded beyond a few academic centers to include physicians and patients in community health settings?
- What mechanisms are in place for innovators to work collaboratively with regulators for designing clinical trials?
- Is there a new paradigm for institutional review boards (IRBs)? Could, for example, the FDA accredit IRBs?
- Can strengthening post-market monitoring and observational data reduce the burden of pre-market evidentiary requirements?
- What are the current mechanisms for reimbursing novel devices? Are there novel strategies for extending coverage?

Unmet Needs and Device Research Prioritization

It is insufficient to simply ensure that all of the pieces to support a healthy medical device innovation enterprise are in place without also considerable thought given to identifying areas of unmet medical need in which novel medical devices could play an important role in care. Currently, the large risk and liability associated with innovation for unmet needs, as well as issues surrounding small patient population size, may disincentivize innovators from moving into spaces with a dearth of appropriate treatment options. A lack of options can force providers to employ medical devices that have not been demonstrated as safe and effective for that indication, as is routine in pediatric interventional cardiology.¹⁰ Systematic assessments of the needs of patient populations, creative strategies for mitigating challenges, and engagement of patients, providers, manufacturers, and others in this process will be crucial. These activities will then form a responsive feedback loop for innovators to ensure that priority therapeutic areas are not left behind.

The workshop's third session will provide participants the opportunity to discuss strategies for moving research and development into underserved therapeutic areas. Topics of interest for this discussion include the following:

- What is the current state of mechanisms for identifying and addressing unmet needs in medical device research? What feasible steps can help prioritize medical device research and development investments for unmet needs?
- How can patient and consumer perspectives on unmet needs be better incorporated into efforts to address unmet needs?
- How might the medical device industry develop and implement a coordinated strategy to address medical device needs?

¹⁰ Sutherell, Jamie S., Russel Hirsch, and Robert H. Beekman III. "Pediatric Interventional Cardiology in the United States is Dependent on the Off-label Use of Medical Devices." *Congenital heart disease* 5, no. 1 (2010): 2-7.

- What incentives exist for medical device companies to prioritize research and development in underserved and smaller markets? What more can be done?
- Market forces often drive the prioritization of research and development, but for smaller markets, what other forces (e.g., government, patient advocates, medical societies) can provide incentives, prioritization and direction?
- For rare diseases and unmet needs, should there be new reimbursement strategies to incentivize innovation?

Next Steps

The Engelberg Center for Health Care Reform has designed this expert workshop to encompass a broad array of challenges to medical device development. By intentionally engaging stakeholders throughout the device ecosystem on these issues and the additional viewpoints that arise during workshop discussion, the Center plans to distill a more concrete, actionable set of follow-on workshops that will enable Brookings and interested collaborators to dig deeper into the underlying inefficiencies in the innovation process and recommend policy solutions to overcome them.