Clinical Trial Strategies for Novel Transcatheter Valves

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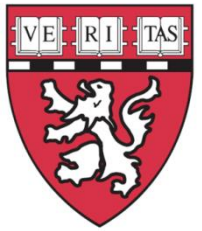

How can clinical trials keep pace with medical device development and improvement?

How can trials be designed to respond to multiple stakeholder needs?

-patients, providers, approval agencies, payors

Medical Technology Innovation Scorecard

Price Waterhouse Cooper assessed 9 countries' capacity and capability for medical technology innovation in 2011: Brazil, China, France, Germany, India, Israel, Japan, UK and US

http://www.pwc.com/us/en/health-industries/health-research-institute/innovation-scorecard/index.jhtml

Medical Technology Innovation Scorecard

•The medical technology innovation ecosystem, long centered in the United States, is moving offshore. *Innovators are going outside the United States to seek clinical data, new-product registration, and first revenue.*

•US consumers aren't always the first to benefit from medical technology and could eventually be last. *Innovators already are going first to market in Europe and, by 2020, likely will move into emerging countries next.*

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Comparison between the US and EU for Approval of Medical Devices

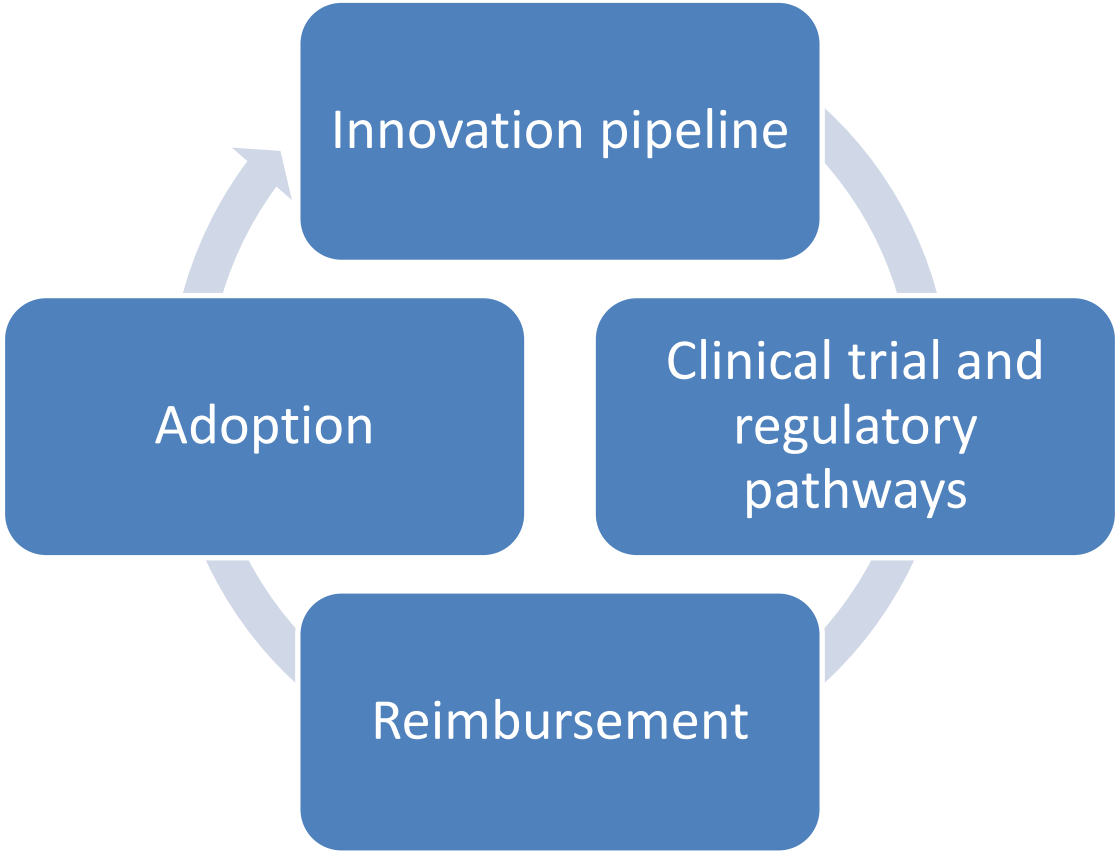
Table 1. Prominent Points of Comparison between the United States and European Union for Approval of Medical Devices.*

System Feature	United States	European Union	Potential Implications
Mandate	Oversight of public health	Device safety (overseen through Competent Authorities), device approval (through Notified Bodies), and facilitation of trade	May influence dealings with industry clients, and attention paid to balance between effectiveness and risk of safety concerns
Centralization	Oversight of all device regulation by the FDA	Directives outline processes carried out by Competent Authorities and Notified Bodies	Standardization and coordination of premarketing and postmarketing evaluation are theoretically simpler and easier to enforce in the United States
Data requirements	Reasonable assurance of safety and effectiveness for approval of high-risk devices, "substantial equivalence" for 510(k) clearance	Generally performance-based analysis, requiring proof that device works as intended	E.U. assessment made by manufacturers and Notified Bodies; provides less insight into clinical end points for high-risk devices
Transparency	Proprietary limits with public reporting of premarketing review of approved devices, recalls, and adverse events	Review of Notified Bodies not made public; postmarketing data shared among Competent Authorities but not with the public	Greater public access to evidence in the United States
Funding	Combination of federal appropriations (80%) and user fees (<20%)	Funding of Competent Authorities variable among countries; Notified Bodies paid directly by sponsors	Notified Bodies may be vulnerable to conflict of interest with industry client; the FDA may be influenced by changes in federal funding and political climate
Access	Clinical premarketing testing of high-risk devices delays patient access to these devices (no differences for low- and moderate-risk devices)	E.U. patients may have access to certain high-risk devices sooner than in the United States, subject to limitations by payers	E.U. patients have faster access to certain devices, but these products are marketed with less rigorous proof of effectiveness and may have a greater chance of later-identified adverse events

* FDA denotes Food and Drug Administration.

Kramer DB et al. N Engl J Med 2012;366:848-855.

Medical Device Innovation in the US



- efficiency, timeliness and reliability

Medical Device Innovation in the US

Practical value of local networks

- Exchange of ideas –basic science, engineering, clinical, health care providers
- Guidance of product development and evaluation
- Operationalizing clinical studies
- Adoption

Devices are Different from Drugs

- Small changes in drug design may lead to off target effects
- Device iterations lead to changes in local effects

What is unique about devices?

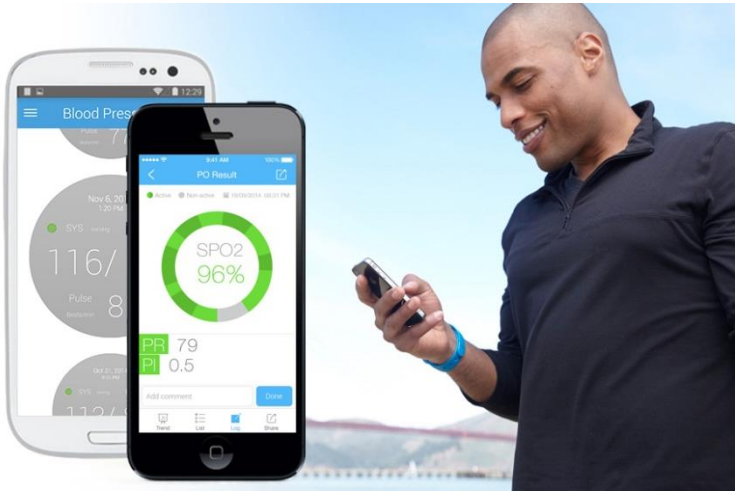
- Iterative improvement based on mechanical design
- Failure mode may be predicted by modelling, bench testing, or detected in single arm safety studies
- Short product life cycle

Range of Appropriate Trial Designs and Trial Strategies

- Objective performance criteria for single arm study comparison (surgical heart valves)
- Open label randomized trial compared with medical therapy with mortality endpoint (percutaneous heart valves)
- Early feasibility single arm studies, post market surveillance single arm registries

Can New “Bigger” Data…

- Decrease cost and complexity of research?
- Facilitate innovation?
- Improve health?



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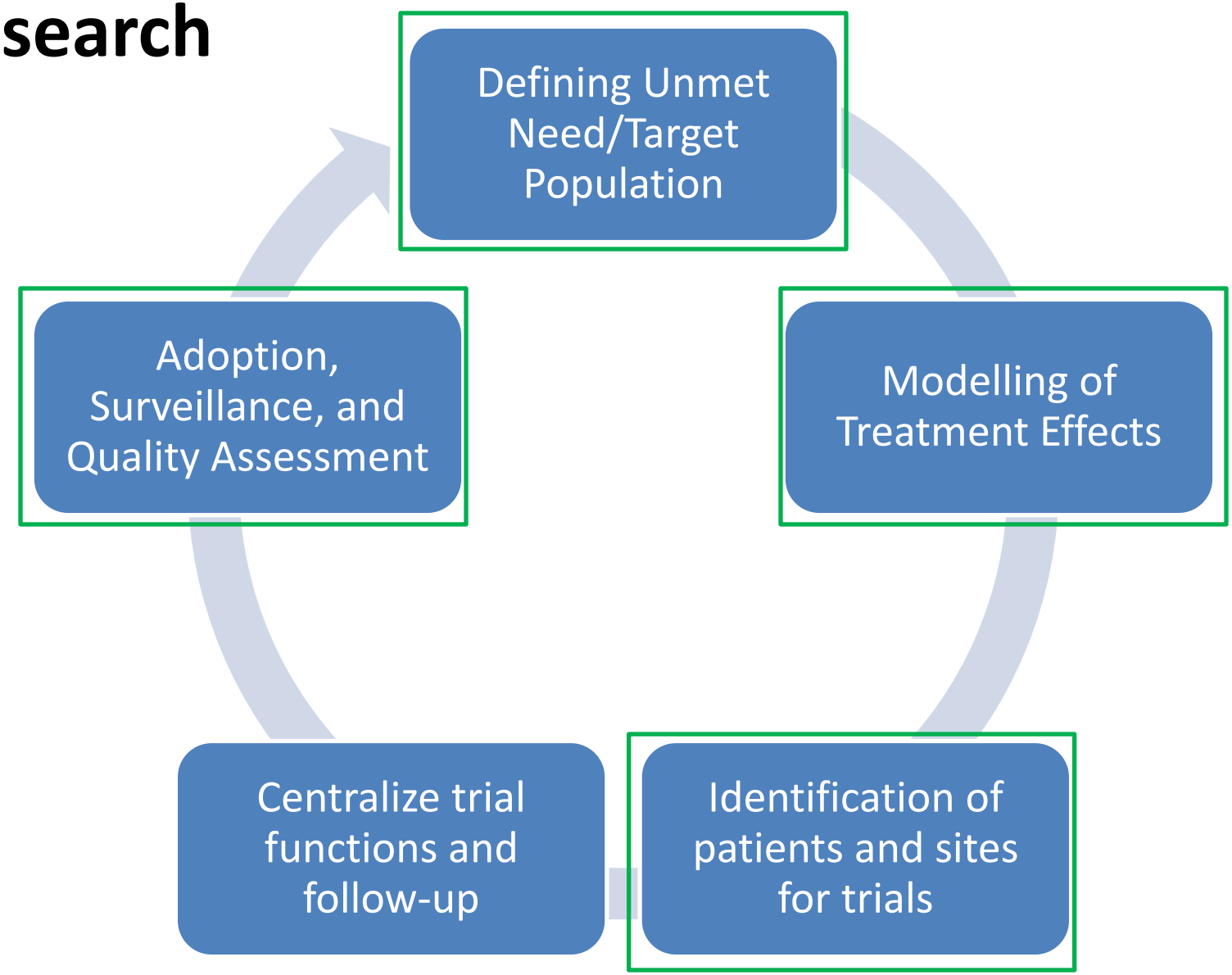
“Bigger” Data Opportunities for Clinical Research



Clinical evaluation of medical devices for valvular heart disease -emerging challenges

1. Best practices for approved technology
2. Defining target population and standard of care (which patients with MR; is TAVR in low risk patients)
3. Impact of concomitant therapies (medical: anticoagulation, antiplatelet; device: CRT, pacing; surgical)
4. Assessing value (to patients, providers, payors)