Title: **Cost of Developing a Therapeutic Complex Medical Device for the U.S. Market**

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Abstract

The U.S. medical device market is the world's largest with an estimated $156 billion in 2019. The FD&C Act requires FDA to approve all new medical devices prior to their introduction to the U.S. market. Manufacturers may obtain FDA approval to market a medical device through one of two routes: 510(k) notification of intent to market or premarket approval (PMA). FDA approves the vast majority of new devices via the 510(k) process, which requires applicants to prove that their devices are substantially equivalent to a legally marketed device. Complex medical devices that are not substantially equivalent to a legally marketed device must receive FDA approval via the PMA process, which requires applicants to demonstrate the device's safety and effectiveness through clinical trials. Very few medical devices enter the U.S. market through the PMA process. In this study, we develop a decision-analytic model of complex medical device development under uncertainty (or risk). Using information from a variety of sources including clinicaltrials.gov, FDA PMA and post-approval study databases, and published literature, we estimate the costs and failure probabilities associated with each stage of development for a complex medical device. Using the model, we estimate the overall cost of development for a complex medical device at $526.4 million after accounting for the cost of failures and the opportunity cost of capital.

Introduction

In the United States, marketing approval for Class III medical devices (i.e., those that support or sustain human life, are of substantial importance in preventing impairment of human health, or which present a potential, unreasonable risk of illness or injury) is granted by the Food and Drug Administration (FDA) through the Premarket Approval (PMA) pathway (U.S. Food and Drug Administration, 2018e).

Therapeutic complex medical devices (CMDs) are one type of Class III medical devices that require PMA applications, as specified under Section 515 of the Federal Food, Drug, and Cosmetic Act (FD&C) (U.S. Food and Drug Administration, 2018d). Examples of therapeutic CMDs include implantable cardiac pacemakers, breast implants, and hemodialysis machines (U.S. Food and Drug Administration, 2018c). Since PMA is the most stringent type of device marketing application required by FDA, there are multiple clinical and non-clinical phases required to bring these types of medical devices to the U.S. market - each with their own associated costs.

Figure 1 shows the various phases involved in developing a therapeutic CMD from "proof of concept" through post-marketing activities (U.S. Food and Drug Administration, 2011; Makower, et al., 2010). There are three non-clinical phases that precede testing of the device in humans. The initial phase of development involves the creation of a "proof of concept" document for a medical need that outlines the steps needed to determine whether the concept is practical (U.S. Food and Drug Administration, 2018c). The next phase

involves building the clinical unit (i.e., the device prototype) for bench and animal testing. Upon successful completion of the prototype, the developer submits an investigational device exemption (IDE) application to FDA to begin clinical studies with human subjects as well as an investigational plan and report of prior investigations for Institutional Review Board (IRB) review and approval. Following IDE and IRB approval, the developer can begin the clinical phase, which includes conducting a feasibility study and a pivotal study. The feasibility study (also known as the first-in-human study or pilot study) is carried out on a small population of patients to obtain preliminary safety and performance information on the therapeutic CMD. If results are favorable, the sponsor undertakes a pivotal study on a larger population of patients to determine the effectiveness of the device as well any possible associated adverse effects. For some PMA applications, multiple feasibility and pivotal studies may be required.

Upon successful completion of these studies, the sponsor compiles all the scientific evidence collected from the clinical studies to demonstrate that the possible health benefits from the intended use of a device outweigh the possible risks and submits a PMA application to FDA for review. If the PMA application is approved, the developer can begin marketing its device in the U.S. Because new safety concerns can emerge once a device is on the market and used by a large population of patients, FDA may also require post-approval studies (PASs) to provide additional safety and effectiveness data (U.S. Food and Drug Administration, 2018c). Data obtained from PASs supplement performance data included in the PMA and may uncover important design, mechanical, electrical, and user related problems not identified in pre-market clinical testing (U.S. Food and Drug Administration,

2018f). Examples of high-risk devices potentially subject to PAS requirements include (1) permanent implants that might cause death or serious injury if they fail and (2) devices used in supporting or sustaining human life.

While there have been recent efforts to quantify the total cost of bringing new drugs to the U.S. market (DiMasi, et al., 2016), limited work has been done to understand the total value of resources used by industry to develop medical devices, and more specifically – therapeutic CMDs. From the peer-reviewed literature, we found only two studies that evaluated characteristics of the different phases of study (e.g., pivotal studies, post-approval studies) conducted along the PMA pathway for devices (Rathi, et al., 2015; Rising & Moscovitch, 2015) and two studies that estimated costs for various parts of the overall PMA process (Makower, et al., 2010; Wimmer, et al., 2016). One study estimated the costs of devices developed by targeted small medical device companies (Makower, et al., 2010) while the other estimated costs associated with PAS phase only (Wimmer, et al., 2016). In this study, we developed a decision-analytic model to estimate the total cost of bringing a therapeutic CMD to the U.S. market accounting for the cost of failures and opportunity cost of capital and using data from various publicly available and proprietary databases, and expert opinion. For additional context, we computed the expected capitalized average cost of developing CMDs inclusive and exclusive of PAS costs.

Methods

Analytic Framework

Using the framework presented in Figure 1, we constructed a decision-analytic model to estimate the expected capitalized cost of developing a therapeutic CMD that takes into the account the cost, duration, the probability of successfully transitioning from one development stage to the next and the opportunity cost of capital using the approach by DiMasi, et al. (2016). We calculated the total expected capitalized cost, *E(CC)*, of developing a given therapeutic CMD exclusive of post-approval study costs as:

$$E(CC) = \sum_{i=1}^{n} E(CC_i)$$

where CC_i = the capitalized cost associated with phase *i* of development and *i* = non-clinical phase, feasibility study phase, pivotal study phase, FDA PMA review/approval phase and

$$E(CC_i) = \frac{1}{p_{i_i}} \times \frac{OOP_i}{\frac{r}{12}} \times \left(e^{\left(\frac{r}{12}\right) \times t_i^b} - e^{\left(\frac{r}{12}\right) \times t_i^e} \right)$$

where *p* is the phase transition success probability from development stage *i* to launch, OOP_i is the out-of-pocket monthly expenditure in 2018 dollars; *r* is the real annual opportunity cost of capital that captures the time value effect; t_i^b is the number of months from the beginning, *b*, of the given stage to product launch, and t_i^e is the number of months from the end, *e*, of the given stage to product launch. The expected total capitalized costs inclusive of capitalized post-approval study costs, $E(CC)_{PA}$, was computed as:

$$E(CC)_{PA} = CC_{PA} + E(CC)$$

Using this general framework and the various data sources listed below, we then estimated the average out-of-pocket costs and expected capitalized average out-of-pocket cost of development for a therapeutic CMD.

Data

We identified various sources of information to estimate our model parameters including the cost and duration for each phase along the PMA pathway (i.e., non-clinical, feasibility study, pivotal study, FDA PMA review, and PAS), as well as phase transition success probabilities and the opportunity cost of capital. These include the Clinicaltrials.gov database maintained by the U.S. National Library of Medicine; FDA's databases on PMA approvals and PASs; a custom tabulation from three of Medidata Solutions' proprietary databases; and the professional opinion of nine medical device experts.

Clinicaltrials.gov is a registry launched in September of 2008 to provide protocol and results information on privately and publicly funded clinical trials conducted around the world. The accompanying and publicly available database is updated daily and contains information on various study parameters (e.g., study start and end dates, number of patients enrolled). For this study, we downloaded the monthly archived data file titled, "20181001_pip-delimited-export.zip" on October 30, 2018, which contained 285,680 unique research studies. Of those records, 32,441 studies had at least one intervention listed as "device." Because not all registered medical device clinical studies are likely to be conducted with the intent to support a PMA application to FDA (e.g., some are conducted for research purposes only), we limited our sample to the 12,271 studies that had at least one sponsor listed as "industry." We then used this subset of studies to define our feasibility study (n=50), pivotal study (n=534), and post-approval study (n=14) samples

using various other data fields available in the clinicaltrials.gov database (e.g., study description, study status, type of study). We constructed these samples following a similar approach as Rathi, et al. (2015) (Figure 2).

FDA makes PMA approval and PAS data available to the public through the FDA website: https://www.fda.gov/Medical-Devices (U.S. Food and Drug Administration, 2018e; U.S. Food and Drug Administration, 2018f). For each approved PMA, FDA's PMA Approvals Database lists the submission and approval dates, supporting clinical study data in the Summary of Safety and Effectiveness information (SSEI) attachment, and product labeling among other fields. For this study, we downloaded data on September 7, 2018 (for the period January 2013 through September 2018) for a total of 191 original PMAs, which included 151 therapeutic devices. The PAS Database provides information on study status and various study protocol parameters (e.g., number of patients enrolled, study design, type of data source [e.g., new data collection, external registry, sponsor registry]), and links each PAS to an approved device by PMA number. We downloaded these data on April 23, 2019 for a total of 718 PASs. Of these, 322 were for devices approved between 2013 and 2018. While 139 of these PASs corresponded to 85 (out of 151) of the therapeutic device PMAs identified for inclusion in this study, only 109 of these corresponding to 73 PMAs required new data collection by the developer. We therefore limited our PAS dataset to these 73 studies.

For clinical trial costs, we used a custom tabulation from three proprietary databases of negotiated investigator grants, outsourcing contracts, and clinical trial sponsors provided

by Medidata Solutions (i.e., Medidata Grants Manager® [PICAS® database], Medidata CRO Contractor® [CROCAS® database], and Medidata Insights™) (Medidata Solutions, 2012). These data cover the period 2004 through 2012 and include average expenditures for the full range of cost elements associated with clinical trials (e.g., cost of IRB approvals, cost of protocols, patient recruitment costs, administrative staff costs). We used available data on the "devices and diagnostics" category to estimate per-patient clinical study costs for our study. Additional information on these data along with assumptions used to extrapolate certain variables are available in Sertkaya, et al. (2016).

Given the dearth of publicly-available data on therapeutic CMD development costs, we also consulted with a panel of nine medical device experts to gain additional insights into the cost, duration, and phase transition success probability associated with the non-clinical phase of therapeutic CMD development. We aggregated responses to create group averages and conducted follow-up interviews to clarify responses and probe further about non-clinical phase nuances, as needed.

Model Parameters

Table 1 presents the parameter estimates, assumptions, and data sources for our therapeutic CMD development cost model. For each study phase, we estimated six different parameters using the data sources described above. In several cases, we relied on more than one data source. For example, when estimating the phase duration of feasibility studies, we linked the studies found in the clinicaltrials.gov database with those in FDA's

PMA Approvals Database. Additional information regarding how and why we used the various sources to estimate each parameter is provided in the technical supplement.

In brief, "phase duration" represents the time it takes to complete a given phase of CMD development. "Start to start" represents the elapsed time in months between the start of one development phase (e.g., the feasibility study phase) supporting a PMA application and the start of the next development phase (e.g., the pivotal study phase) supporting the same application. The "number of patients enrolled" represents the average number of patients enrolled during a given clinical study (feasibility, pivotal, or PAS). The "per-patient cost" represents the average cost that a sponsor incurs per-patient in a clinical trial study in 2018 dollars. The "out-of-pocket costs" represent the average out-of-pocket expenses (not adjusted for failures or cost of capital) a developer incurs during a given therapeutic CMD development phase. The "transition success probabilities" reflect the probability of a sponsor successfully moving from one phase of therapeutic CMD development to the next. For example, if there are 100 therapeutic CMDs at the feasibility phase and only 30 of these CMDs successfully complete their feasibility studies and subsequently begin pivotal studies, then our transition success probability from feasibility study phase to pivotal study phase is 30 percent. Finally, the real opportunity cost of capital (ROCC) represents the rate of return (net of inflation) that the developer would otherwise be able to earn at the same risk level as the investment in the new therapeutic CMD that has been selected. This value varies significantly by developer-specific factors (e.g., product portfolio, size of company) and other exogenous factors (e.g., economic and regulatory climate for device development projects). According to a study by Harrington (2012), the estimated value for the medical

device sector ranges from a low of 9.2 percent to a high of 11.4 percent. In our model, we used 10.4 percent as the average real opportunity cost of capital.

Results

We estimated the average out-of-pocket cost of developing a therapeutic CMD at around $54 million before conducting PASs, and approximately $60 million after accounting for PASs (Table 2). For the cost excluding PASs, 37 percent was non-clinical phase related, 60 percent was clinical phase (i.e., feasibility and pivotal study) related, and the remaining 3 percent was associated with the FDA PMA phase. When capitalized to account for the opportunity cost of capital and after accounting for the costs of failures (i.e., costs associated with those devices that reach a given development phase but not to market), expected capitalized average development cost was estimated at approximately $522 million before conducting PASs and $526 million after conducting them.

From an expected capitalized cost perspective in which both cost of failures and opportunity cost of capital are accounted for, the share of total expected development cost represented by the non-clinical phase is around 85 percent, regardless of whether post-approval costs are included. This means that the non-clinical phase represents the largest portion of total expected capitalized development costs, primarily because the probability of moving from non-clinical phase to a marketable therapeutic PMA device is only 14 percent. Yet, as the developer successfully transitions from one development phase to another, the likelihood of approval increases. For example, the odds of a device making it to

market is significantly higher if the device has already cleared the feasibility study phase than one that is at the proof-of-concept development phase.

This means that even though a large, pivotal clinical study may be more expensive out-of-pocket than non-clinical work (i.e., proof of concept development, prototype development and bench testing), the device has a greater chance of making it to market once this phase is reached.

The clinical phases of device development (feasibility and pivotal) also contribute substantially to total out of pocket development costs, comprising around 60 percent of total costs. From a capitalized out-of-pocket cost perspective, clinical development comprises 41 percent of total capitalized development costs, excluding post-approval costs but including the time value of the investment. From an expected capitalized out-of-pocket cost perspective, the share of total expected capitalized development costs represented by clinical development is around 15 percent, excluding post-approval costs.

The pivotal clinical phase represents the majority of clinical development costs, due primarily to enrolling large number of patients (565 on average versus 42 for feasibility studies), taking twice as long as feasibility studies (57 months versus 28 months), and greater out-of-pocket costs (approximately $31 million vs. $1.4 million). Rising and Moscovitch (2015) reported a comparable estimate of study duration (median=3 years) and a slightly lower estimate for sample size (median enrollment =297 patients) for pivotal studies from their review of 27 approved devices. Rathi, et al. (2015) also estimated

median enrollment for medical device studies via the PMA Approval pathway and reported similar results for 52 feasibility studies (median=65), 30 pivotal studies (median=241) and 33 PASs (median=222 patients).

Discussion

To our knowledge, this study represents the only bottom-up analysis of therapeutic CMD development costs. The only related studies we could identify during our literature search and discussions with industry experts include a survey conducted by Stanford University researchers in 2010 on the impact of FDA on medical device innovation in the United States, an estimate of PAS costs for medical devices, and an assessment of costs required to develop new drugs (Makower, et al., 2010; Wimmer, et al., 2016; DiMasi, et al., 2016).

Makower, et al. (2010) surveyed 204 medical device companies and asked the respondents to reflect on their experiences during the clinical development process. The average out-of-pocket cost of developing a medical device that requires a PMA application to FDA was estimated around $94 million ($119 million in 2018 dollars). Of these costs, around 30 percent was non-clinical phase related, 50 percent was clinical phase related and the remaining 20 percent was for getting FDA PMA approval for marketing the device in the U.S. The study did not provide costs associated with any PASs that developers may need to conduct after obtaining PMA approval. Further, the estimates reported in the study were based on a survey of 204 small medical device companies in the U.S. As such, this estimate is not directly comparable to our estimate of $526 million (total expected capitalized cost,

252 including post-approval studies). Makower, et al. (2010) did not incorporate the cost of
253 failures or the opportunity cost of capital and appears to have only included the out-of-
254 pocket cash layout, which we estimate at $54.0 million (i.e., sum of $20 million for non-
255 clinical, $1.4 million for feasibility study, $30.7 million for pivotal study, and $1.9 million
256 for PMA approval phases) excluding PASs with our model. The different results of the two
257 studies can be attributed to differences in methodology, scope (therapeutic CMDs versus
258 devices developed by targeted small medical device companies), and what is considered as
259 a development cost. For example, Makower, et al. (2010) included operational costs
260 incurred during FDA review as part of the PMA approval costs whereas we excluded those
261 in our study. While such costs may be applicable to small device manufacturers with a
262 single product in development, we did not think that this would be the case for medium to
263 large device manufacturers with an established revenue stream from their currently
264 marketed devices. Further insights to the differences in the estimates would require a
265 closer analysis of the survey instrument used and the data collected by those researchers.
266
267 Wimmer, et al. (2016) developed a cost estimation model to estimate the cost of PASs for
268 medical devices using information gathered from integrative structured interviews with
269 twelve domain experts from the clinical trial design arena. This model was applied to 277
270 PASs initiated between March 2005 through June 2013 and cost estimates were developed
271 to reflect the budgeted costs that would be anticipated if the study was conducted as
272 originally planned. The researchers estimated a median cost of approximately $2.2 million
273 ($2.3 million in 2018 dollars) per study. In our study, we estimated an average PAS out-of-
274 pocket cost of about $6.0 million.

DiMasi, et al. (2016) estimated the resources expended by industry to discover and develop 106 randomly selected new drugs from a survey of 10 pharmaceutical firms. These data were used to estimate the average pre-tax cost of new drug and biologics development. To do so, the researchers linked the costs of compounds abandoned during testing to the costs of compounds obtaining market approval. DiMasi et al (2016) estimated the total out-of-pocket cost per approved new drug at $1,395 million ($1,581 in 2018 dollars) while the expected capitalized out-of-pocket cost was estimated at $2,558 million ($2,900 million in 2018 dollars), excluding post-approval costs. Adding the estimated cost of post-approval research and development increased the expected capitalized out-of-pocket cost to $2,870 million ($3,253 in 2018 dollars).

Our study has several limitations that need mention. First, we were not able to identify and use all clinical studies of therapeutic CMDs in clinicaltrials.gov and hence were limited to small convenience samples for which data elements for the listed studies were mostly complete and likely coded correctly. Further, we were unable to identify and eliminate those clinical studies that might have been for a 510(k) FDA application (instead of a PMA). This may have resulted in underestimates of such parameters as average number of patients and study duration for 510(k) device studies, when required, are not as onerous as those required for a novel therapeutic device. Nonetheless, our approach to selecting our convenience sample of studies is similar to those used by other researchers who have characterized different features of the various study phases along the PMA pathway (Rathi, et al., 2015). Second, the non-clinical phase duration and associated costs are based on

expert opinion as there are no reliable sources of publicly available information on this early development phase. Expert opinion is subject to multiple heuristic biases including availability, representativeness, and anchoring, among others. While we tried to minimize the potential for such biases by interviewing a sizable pool of experts, we acknowledge that expert opinion is not a substitute for rigorous empirical methods. Finally, the degree of complexity across different therapeutic CMDs is highly variable. For example, an implantable artificial kidney is likely to be orders of magnitude more costly to develop than a hemodialysis machine. Thus, we expect there to be a large degree of variability around the average development costs we estimated in this study.

Conclusions

We conducted the first analysis of the costs of therapeutic CMD development through the PAS phase accounting for the costs of failures and the opportunity cost of capital. Bringing a therapeutic CMD to the U.S. market costs around $526.4 million inclusive of post-approval studies. The non-clinical development phase constitutes the largest portion of these costs (85 percent) with FDA review phase accounting for only a small fraction (0.5 percent). Even though therapeutic CMD development is a costly endeavor, resources expended for development pale in comparison to those for new drug development, which is more than 6 times costlier according to recent estimates (DiMasi, et al., 2016).

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Figure 1. Therapeutic CMD Development Phases

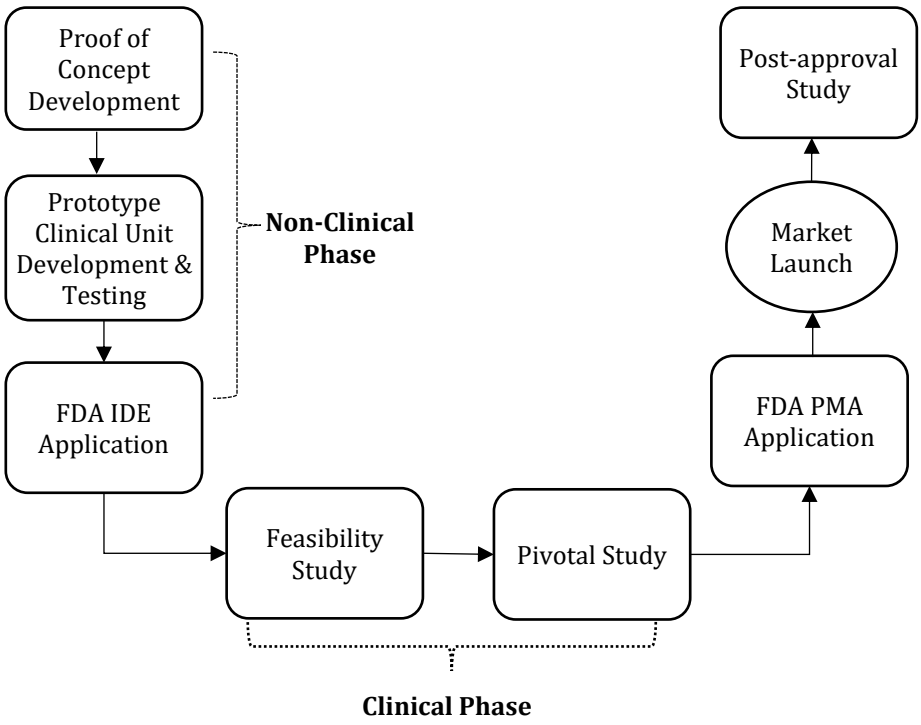
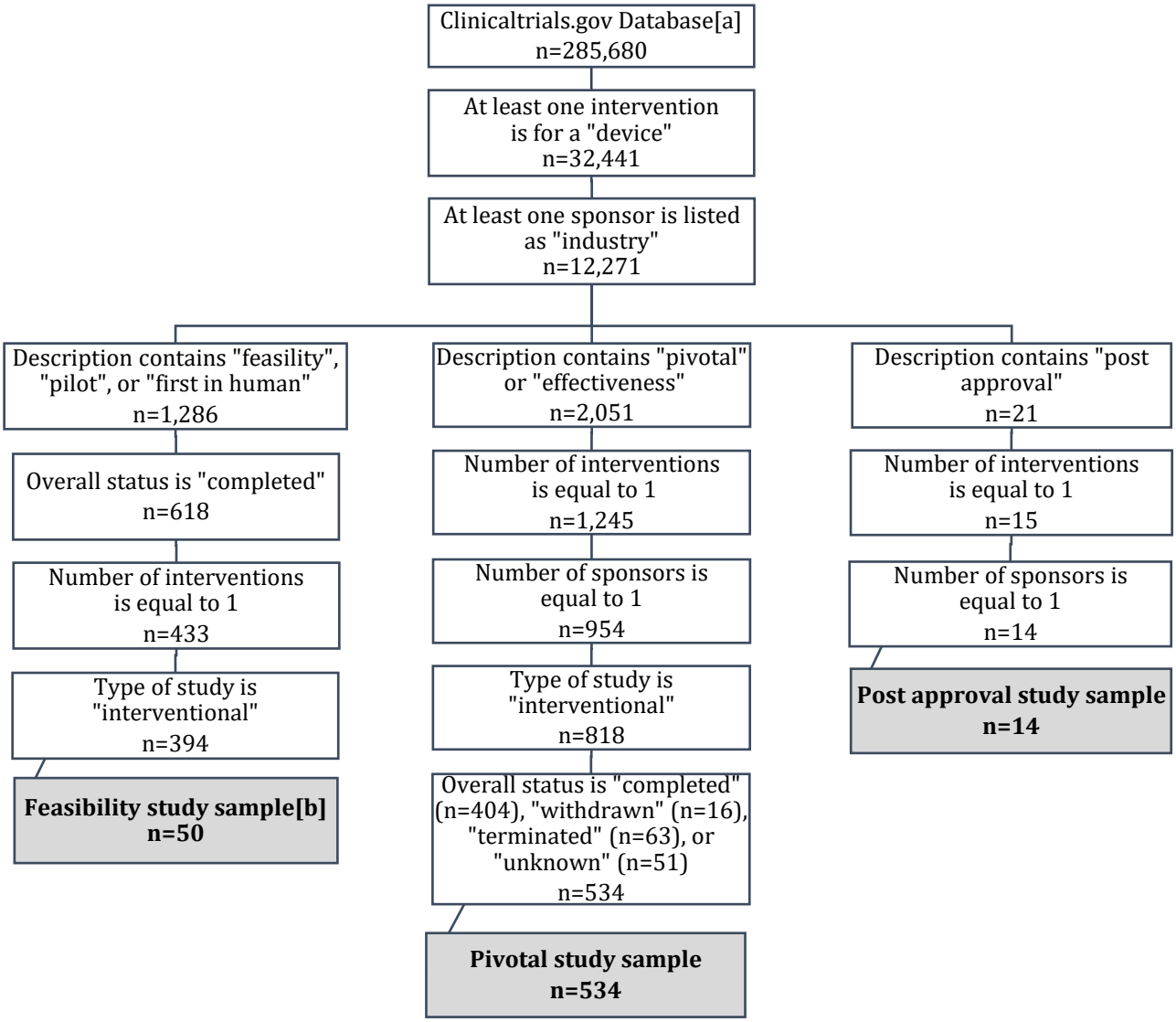


Figure 2. Identification of Feasibility, Pivotal, and Post-Approval Studies from Clinicaltials.gov Database



Notes:
[a] Data were extracted from the clinicaltrials.gov database on October 30, 2018.
[b] The 50 studies that we could be reasonably sure were, in fact, feasibility studies for medical devices constitute our feasibility study convenience sample. This selection was based on manual review of detailed study descriptions for the 394 "interventional" studies identified in the clinicaltrials.gov database.

Table 1. Summary of Therapeutic CMD Development Cost Model Parameters and Assumptions

Parameter	Phase	Value	Source
Phase Durations (in months)	Non-clinical	60.0	Expert opinion
	Feasibility study	28.0	Clinicaltrials.gov feasibility study and FDA PMA approval samples
	Pivotal study	56.9	FDA PMA approval sample
	FDA PMA review	17.4	FDA PMA approval sample
	Post-approval study	81.2	Clinicaltrials.gov post-approval study sample
Start to Start (in Months)	Non-clinical to feasibility study	60.0	Expert opinion
	Feasibility study to pivotal study	37.2	Clinicaltrials.gov feasibility study sample
	Pivotal study to FDA PMA submission	42.4	FDA PMA approval sample
	FDA PMA submission to approval	17.4	FDA PMA approval sample
Number of Patients Enrolled	Non-clinical	NA	Not applicable
	Feasibility study	42	Clinicaltrials.gov feasibility study and FDA PMA approval samples
	Pivotal study	565	FDA PMA approval sample
	FDA PMA review	NA	Not applicable
	Post-approval study	414	FDA PAS sample
Per-patient Cost (in $ 2018)	Non-clinical	NA	Not applicable
	Feasibility study	$34,059	Medidata Solutions, 2012
	Pivotal study	$54,332	Medidata Solutions, 2012
	FDA PMA review	NA	Not applicable
	Post-approval study	$14,416	Medidata Solutions, 2012
Out of Pocket Costs (in $ 2018)	Non-clinical	$20,000,000	Expert opinion
	Feasibility study	$1,428,249	Calculation
	Pivotal study	$30,672,652	Calculation
	FDA PMA review	$1,852,816	AdvaMed, 2014
	Post-approval study	$5,961,197	Calculation
Transition Success Probabilities (%)	Non-clinical to feasibility study	46.9%	Expert opinion
	Feasibility study to pivotal study	48.0%	Clinicaltrials.gov feasibility study sample
	Pivotal study to FDA PMA submission	75.7%	Clinicaltrials.gov pivotal study sample (estimated as the ratio of completed studies, 404, to all pivotal studies sampled, 534, assuming all completed studies will proceed to FDA PMA phase)
	FDA PMA submission to approval	80.5%	U.S. Food and Drug Administration, 2018b
Opportunity Cost of Capital (%)		10.4%	Harrington, 2012

Table 2. Expected Average Cost of Developing a Therapeutic CMD for the U.S. Market

Phase	Probability of FDA Approval from Given Phase [a]	Out-of-Pocket Costs (in million $ 2018) [b]		Expected Out-of-Pocket Costs (in million $ 2018) [c]		Capitalized Out-of-pocket Costs to Date of Launch (in million $ 2018) [d]		Expected Capitalized Out-of-pocket Costs (in million $ 2018) [e]	
		$	%	$	%	$	%	$	%
Non-clinical	14%	$20,0	37%	$145.7	72%	$60.8	57%	$442.8	85%
Clinical (Feasibility and Pivotal Phases)	NA	$32,1	59%	$55.2	27%	$43.6	41%	$76.8	15%
Feasibility Study	29%	$1.4	3%	$4.9	2%	$2.9	3%	$10.0	2%
Pivotal Study	601%	$30.7	57%	$50.4	25%	$40.6	38%	$66.7	13%
FDA PMA Approval	801%	$1.9	3%	$2.3	1%	$2.0	2%	$2.5	0.5%
Post-approval Study [f]	NA	$6.0	NA	$6.0	NA	$4.3	NA	$4.3	NA
Total (without post-approval study costs)	**NA**	**$54.0**	**100%**	**$203.3**	**100%**	**$106.4**	**100%**	**$522.1**	**100%**
Total (with post-approval study costs)	**NA**	**$60.0**	**NA**	**$209.2**	**NA**	**$110.6**	**NA**	**$526.4**	**NA**

Notes:
NA = Not applicable
Values may not add up due to rounding.
[a] The figure represents the transition probability from the given phase to approval.
[b] These are the raw out-of-pocket expenses not adjusted for opportunity cost of capital or failures.
[c] These figures represent the out-of-pocket expenses after adjusting for the cost of failures computed as the raw out-of-pocket cost divided by the transition success probability. Expected out-of-pocket costs take into account the costs of failures but not the opportunity cost of capital.
[d] These figures represent the out-of-pocket costs at the point of launch after adjusting for the opportunity cost of capital. Capitalized out-of-pocket costs take into account the opportunity cost of capital but not the costs of failures.
[e] Expected capitalized costs take into account the costs of failures and the opportunity cost of capital.
[f] Post-approval costs include pivotal study follow-up costs incurred after the PMA is approved. In the current model (without diagnostic devices), however, these follow-up costs are zero.

TECHNICAL SUPPLEMENT

The following sections discuss the basis for the model parameter estimates presented in Table 1.

Phase Durations

The phase duration parameter refers to the time it takes to complete a given stage of development depicted in Figure 1. For the non-clinical stage, our estimate of 60 months represents the time it takes for proof of concept development, clinical unit development, and obtaining an IDE, which is required by FDA to test the safety and efficacy of unapproved medical devices in human subjects.

We derived our feasibility study phase estimate of 28 months by combining the 50 feasibility studies from our clinicaltrials.gov sample with the 29 feasibility studies from our FDA PMA approvals database sample, removing the duplicate studies (one study), and taking the average feasibility study duration from the combined sample.

Our pivotal and FDA PMA review duration estimates were derived using study duration data from the FDA PMA database. Our post-approval phase duration estimate of 81.2 months is based on the average study duration from our sample of 14 post-approval studies we identified in the clinicaltrials.gov database. We had to rely on the

clinicaltirals.gov post-approval study sample because the FDA PAS database did not publicly report the start and end dates for the completed PASs they have listed.

Time from Phase Start to Next Phase Start

The start to start parameter refers to the elapsed time between the start of one development phase (e.g., feasibility study phase) supporting a PMA application and the start of the next development phase (e.g., pivotal study phase) supporting the same application. For the non-clinical phase to feasibility study phase estimate, we used the same 60-month interval estimated for the non-clinical phase duration; that is, we assumed feasibility testing will begin immediately upon successful completion of the non-clinical development phase.

For the feasibility study phase to pivotal study phase estimate of 37.2 months, we used the clinicaltrials.gov feasibility study sample. First, we matched the feasibility studies in our sample with pivotal studies in our database based on an examination of the device names, descriptions, and sponsors. Because not all feasibility studies successfully proceed to the pivotal phase, we were able find matching pivotal studies for 48 percent (24 out of 50) of studies in our feasibility sample. Next, using the study start date field, we then computed the difference between the start date for the feasibility study and the start date of the pivotal study in our matched sample (24 studies). The average time from feasibility phase start to pivotal phase start represents the average value for these 24 studies in our matched sample.

To calculate the time from pivotal-phase start to FDA PMA submission we relied on our FDA PMA approval sample of 151 unique PMAs of which 149 had pivotal study data reported in their SSEIs corresponding to a total of 209 pivotal studies.[1] We computed the difference in the reported FDA PMA submission date and pivotal study start date for each of the 209 pivotal studies. The average time from pivotal study start date to FDA PMA submission date, 42.4 months, represents the average value for these 209 studies in our FDA PMA approvals sample.

Similarly, we relied on our FDA PMA approvals sample that consists of 151 PMA approvals with information on PMA submission and approval dates to estimate the average time it takes from FDA PMA submission to PMA approval (17.4 months).

Average Number of Patients Enrolled

The patient enrollment parameter represents the average number of patients enrolled during a given clinical study (feasibility or pivotal) phase supporting a PMA application which is one of the key drivers of the cost of a clinical study. We derived our feasibility study estimate of 27.47 patients using the 78 studies from our combined feasibility and FDA PMA approval samples. Next, we estimated that on average, a developer conducts 1.53

[1] Some of the 149 PMA submissions included information on more than one pivotal study in their SSEIs. Of the 149 PMAs with supporting pivotal study information, 79 percent reported one pivotal study, 13 percent reported two, and the remaining 8 percent reported three or more pivotal studies in their SSEIs.

feasibility studies per PMA based on the 19 PMAs that provided information on the feasibility studies conducted in their SSEIs. This translated to an estimate of 42 patients (≅ 27.47 × 1.53) for the feasibility study phase.

For our pivotal study phase estimate, we first averaged the number of patients enrolled in the 209 pivotal studies as reported in our FDA PMA approvals sample to estimate the number of patients per pivotal study at 402.47. Next, we estimated that on average, a developer conducts 1.40 pivotal studies per PMA based on the 149 PMAs that provided information on the pivotal studies conducted in their SSEIs. This translated to an estimate of 565 patients (≅ 402.47 × 1.40) for the pivotal study phase.

We used the FDA PAS data to estimate the average number of patients for the post-approval study phase. Of the 151 PMAs in our sample, FDA requested post-approval studies that require collection of new data by the sponsor at the time of PMA approval for 73 PMAs. However, only 67 of the 73 PMAs contained planned patient enrollment data for the associated PASs. The average number of planned patient enrollment for the post-approval study phase among the 67 PMAs with associated PASs was 895 patients. Given the 46 percent probability of FDA requiring a PAS involving new data collection from a sponsor at

the time of PMA approval,[2] we estimated the average number of patients for the post-approval study phase at 414 (≅ 895 × 0.46).

Average Per-Patient Costs

The per-patient cost parameter represents the average cost a sponsor incurs per-patient in a clinical trial study supporting a PMA application. Our per-patient cost estimates are based on the estimates we had obtained from Medidata Solutions for the "devices and diagnostics" therapeutic area.

We used the Phase 1 per-patient costs reported by Medidata Solutions as an estimate for therapeutic CMD feasibility study per-patient costs. We assumed that the per-patient costs for a therapeutic CMD pivotal study are equivalent to the average of Phase 2 and Phase 3 per-patient costs reported by Medidata Solutions. For our post-approval study per-patient cost estimate, we used $14,416 reported by Medidata Solutions for a Phase 4 study.

Out-of-Pocket Costs by Stage of Development

[2] Computed as the ratio of 67 PMAs with PAS requirement involving new data collection and reported number of planned patients to 145 PMAs (= 151 PMAs – 6 PMAs without reported number of planned patients for their PASs).

The out-of-pocket cost parameter represents the average out-of-pocket expenses (not adjusted for failures or cost of capital) a developer incurs during a given therapeutic CMD development phase. Our literature review to date did not identify any studies that report out-of-pocket expenditures by phase for therapeutic CMDs. We relied on expert opinion provided by the expert panel coupled with focused follow-up interviews we conducted with medical device experts to estimate the out-of-pocket costs for non-clinical phase at $20 million. The experts interviewed reported a range of costs for this stage with $15 million for the lower bound for less complex therapeutic devices with a clear development path to as high as $35 million for those that are highly complex innovative implantable devices.

We estimated the out-of-pocket costs for the feasibility, pivotal, and post-approval study phases as the product of average number of patients enrolled (42 for a feasibility, 565 for a pivotal, and 895 for a post-approval study when such a study is required[3]) and per-patient costs ($34,059 for a feasibility, $54,332 for a pivotal, and $14,416 for a post-approval study) at $1.4 million, $30.7 million, and $6.0 million,[4] respectively.

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[3] The model uses the expected number of patients enrolled for a PAS which is the product of 895 patients per study and the 46 percent chance that a PAS would be required by FDA; 414 (≅ 895 × 0.46).

[4] According to Wimmer, et al. (2016) the median cost of a PAS study is $2.22 million ($2.15 million in $ 2016) with a range of $1.38 million to $12.78 million based on estimates generated by a panel of 12 medical device experts. Since FDA on average requires 1.5 PAS studies per PMA for those PMAs deemed to need a PAS, this translates to a median cost of $3.33 million for the PAS stage, roughly half of what we estimated using FDA data on PAS study enrollment and per-patient cost information from Medidata Solutions databases.

Our FDA PMA review phase out-of-pocket cost estimate of approximately $1.9 million is based on AdvaMed's 2014 docket submission for FDA's proposed rule on Medical Device Classification Procedures (FDA-2013-N-1529) (AdvaMed, 2014). In its submission, AdvaMed noted that "total average costs of supporting a PMA" would include $900,000 for panel meeting preparation, $475,000 for PMA submission preparation, $125,000 for pre-approval inspection, and additional costs for MDUFA user fees estimated as the average of $322,147 standard MDUFA fee and $80,537 small business MDUFA fee (U.S. Food and Drug Administration, 2018a). Inflating these 2014 figures to 2018 dollars, we estimated the out-of-pocket costs for the PMA review phase at around $1.9 million.

Phase Transition Success Probabilities

The phase transition success probability parameter represents the probability of a developer successfully moving from one stage of therapeutic CMD development to the next. For example, if there are 100 therapeutic CMDs at the feasibility stage and only 30 of these CMDs successfully complete their feasibility studies and subsequently begin pivotal studies, then our transition success probability from feasibility study phase to pivotal study phase is 30 percent (= 30 ÷ 100).

Given the lack of publicly available information on the non-clinical stage of development, we relied on expert opinion elicited from our panel of experts combined with more focused discussions with medical device experts to estimate the probability of successfully transitioning from the non-clinical stage to the feasibility stage at 47 percent, which

represents the simple average of estimates ranging from 15 to as high as 90 percent provided by our panel of nine medical device experts. The estimate is intended to represent the transition probability for a single investigational device design and does not capture the iterative nature of the early development stage for therapeutic CMDs where the sponsor might revise the design of the prototype, intended use, or other characteristics.

We estimated the transition probability from the feasibility study phase to pivotal study phase as the ratio of our feasibility sample subset with matching pivotal studies (24 studies total) to the full feasibility sample of 50 studies to be 48 percent (= 24/50).

To estimate the probability of successfully transitioning from the pivotal-study phase to FDA PMA submission phase, we again relied on clinicaltrials.gov data, but employed a different methodology. We identified 534 pivotal medical device studies in the clinicaltrials.gov database. Of these 534 studies, 63 were terminated, 16 were withdrawn, 51 had unknown resolutions, and 404 were completed. First, we assumed that the completed studies are successful in demonstrating the safety and effectiveness of the medical device being investigated. We further assumed that 100 percent of such successful studies is used in support of a PMA application. Thus, we estimated the probability of successfully transitioning from the pivotal study phase to the FDA PMA submission phase as the ratio of the 404 completed studies to the total sample of 534 at 75.7 percent.

Our FDA PMA submission to PMA approval transition success probability of 80.5 percent (i.e., the percent of original PMA applications submitted to FDA that are approved) is based

on MDUFA IV CDRH performance data as of August 2018 reported by FDA (U.S. Food and Drug Administration, 2018b). MDUFA quarterly updates report the percent of original PMAs approved by CDRH from 2001 to August 2018 annually (see Table 3). We used the historical average of 80.5 percent (with a median of 82 percent) to represent the FDA submission to approval probability.

Opportunity Cost of Capital

The real opportunity cost of capital (ROCC) represents the rate of return (net of inflation) that the developer would otherwise be able to earn at the same risk level as the investment in the new therapeutic CMD that has been selected. The value of ROCC varies significantly by sponsor-specific factors, such as product portfolio and size of company, as well as other exogenous factors, such as economic and regulatory climate for device development projects. According to a study by Harrington (2012), the estimated ROCC for the medical device sector ranges from a low of 9.2 percent to a high of 11.4 percent. In the model, we use 10.4 percent as the average real opportunity cost of capital.

Table 3. FDA PMA Approvals from 2001 through August 2018 (Downloaded from FDA Website on November 9, 2018)

Year	Percent of Original PMAs Approved [a]
2001	82.0%
2002	72.0%
2003	86.0%
2004	82.0%
2005	90.0%
2006	82.0%
2007	76.0%
2008	81.0%
2009	68.0%
2010	59.0%
2011	71.0%
2012	70.0%
2013	85.0%
2014	86.0%
2015	95.0%
2016	89.0%
2017	91.0%
2018	84.0%
Mean	**80.5%**
Median	**82.0%**
Standard Deviation	**9.1%**

[a] From Quarterly Update on Medical Device Performance Goals - MDUFA IV CDRH Performance Data - Action through 30 June 2018
[b] Reflects 8 months of data in 2018.

Table 4. Real Opportunity Cost of Capital (ROCC) Estimates from Harrington (2012)

Estimation Method	Firm Size	Study Period	Sample Size	Real COC
CAPM [a]	All	2001-2005	44	9.6%
	All	2006-2008	42	11.2%
	Large	2001-2005	12	9.2%
	Large	2006-2008	15	10.9%
	Small	2001-2005	32	9.8%
	Small	2006-2008	27	11.4%
			Average	**10.4%**

[a] CAPM = Capital asset pricing model