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THERAPEUTIC COMPLEX MEDICAL DEVICE DEVELOPMENT

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LIST OF ACRONYMS

ACA	Affordable Care Act
ASPE	Office of The Assistant Secretary for Planning and Evaluation
CMD	Complex medical device
CROs	Contract research organization
CTTI	Clinical Trials Transformation Initiative
DHHS	Department of Health and Human Services
eNPV	Expected net present value
EHR	Electronic health record
ERG	Eastern Research Group, Inc.
FDA	Food and Drug Administration
FIH	First in human
IRB	Institutional review board
MDUFA	Medical Device User Fee Amendments
NIH	National Institutes of Health
NPV	Net present value
OCOC	Opportunity Cost of Capital
PMA	Premarket Approval
POS	Probability of success
SDV	Source data verification

EXECUTIVE SUMMARY

The cost of bringing a medical product to the U.S. market has been increasing and clinical trials constitute a large portion of these costs. For complex medical devices that require a Premarket Application (PMA) submission to FDA, clinical trial costs account for between 50 to 60 percent of total R&D expenditures (Makower, et al., 2010; Sertkaya, et al., 2022). Clinical trials contribute significantly to the rising cost trend as they have become more expensive, complex, and lengthier over time. Thus, there is ongoing interest in reducing the overall cost of medical product development by improving the efficiency of clinical trials conducted in support of regulatory submission for marketing approval.

This study quantified the potential impacts of the following strategies on the cost, duration, and phase transition probability associated with therapeutic complex medical device development stages:

- **Mobile technologies—**Mobile technologies can include cell phones, wearable trackers, and other devices that capture data directly from patients. Electronic data capture means capturing study data in electronic format. The strategy could entail encouraging the use of mobile and other technologies in clinical trials and the development process as a whole and clarifying requirements around their use.

- **Simplified clinical trial protocols and reduced amendments—**The strategy could entail encouraging sponsors to simplify clinical trial protocols, where possible, ensuring that they have a clear understanding of what is required by FDA and what is superfluous.

- **Reduced source data verification (SDV)—**Source data verification is the process of comparing data collected throughout the clinical trial to the original source of information to verify data integrity. The strategy could entail engaging sponsors in discussions on the topic of data and site monitoring to ensure that they are aware of the FDA guidance stating that 100 percent source data verification is not required, as well as continuing to educate reviewers on this policy.

- **Improvements in FDA review efficiency and interactions—**The strategy could entail providing more opportunity to identify, discuss, and resolve substantive issues during the review, continuing to educate FDA reviewers on changes in FDA policy, and providing more transparency about what endpoints are required. However, the strategy does not account for the additional resource burden on FDA associated with implementing these strategies.

- **Staged approval—**Staged approval could entail granting provisional marketing approval to market a drug, complex medical device, or preventive vaccine after safety and basic efficacy have been shown, and then continuing to collect additional safety and efficacy data. This would reduce the threshold for initial approval,

perhaps with a limited patient population, and then gradually expand it as more data are collected.

- **Biomarkers as surrogate endpoints—**Biomarkers as surrogate endpoints are biological indicators that may correlate with the desired clinical endpoint, for example when it would take a long time for the clinical endpoint to become evident. The strategy could entail clarifying the path to biomarker validation or encouraging collaboration between academics, public entities, and industry to develop and validate biomarkers for use as surrogate endpoints.

- **Electronic health records—**EHRs, used here as being synonymous with electronic medical records (EMRs), are digital versions of the data collected when a patient visits a healthcare provider's office. The strategy could entail encouraging sponsors to use EHRs for patient and physician recruitment or to collect clinical endpoints.

- **Patient registries—**A patient registry is an organized system that uses observational study methods to collect uniform data to evaluate specified outcomes of a disease or condition for a population. Registries include those established by a patient organization for a particular disease as well as registries that are sometimes established by the manufacturer and used as a post-marketing study. The strategy could entail encouraging sponsors to use registry data for patient and physician recruitment or to collect clinical endpoints for use in a clinical trial, where possible.

- **Adaptive design—**An adaptive design allows modifications to the trial and/or statistical procedures of the trial after its initiation without undermining its validity and integrity. The strategy could entail clarifying FDA's policies on whether certain types of adaptive trial design are acceptable and encouraging their use.

- **Standardized contracts—**Standardized contracts are contract templates for use in sponsor-initiated multi-site trials, intended to reduce the complexity and duration of contract negotiations for clinical trial studies. The strategy could entail encouraging the use of master contracts and standardized contracts or compiling existing resources into a central location.

- **Centralized IRBs[1]—**A centralized Institutional Review Board is a single IRB of record for all clinical trial sites in a multi-center trial, which would remove the need to obtain approvals from multiple local IRBs. The strategy could entail encouraging the use of centralized IRBs, which may involve creating guidance or other educational material and encouraging local IRBs not to require local IRB approval.

[1] FDA issued regulations and guidance on the use of centralized IRBs in multi-institutional drug studies back in 2006. Additionally, in 2016, the 21st Century Cures Act removed the requirement for review by "local" IRB for device studies, thereby making it possible to use centralized IRBs in medical device trials. While the use of centralized IRBs has gained widespread adoption in drug development programs, their use in medical device trials remains low.

The strategies listed above were identified in ERG (2022) via a literature review conducted during the 2016-2018 period. Since that time, several of the strategies included herein were adopted and additional strategies have emerged, such as remote patient monitoring and virtual visits, which gained widespread adoption due to the COVID-19 pandemic. Additionally, recognizing the challenges of conducting clinical trials during a public health emergency, FDA issued a new guidance containing nonbinding recommendations on a range of issues, including the use of virtual patient visits, remote monitoring of clinical sites, and use of real-world data in regulatory submissions (U.S. Food and Drug Administration, 2021a). Given the timing of the literature review and analyses, this report does not address these new developments.

To facilitate the evaluation of the above-mentioned strategies, the study also included the development of a cost model for therapeutic complex medical devices. The model used data from a variety of sources (public and non-public) and widely accepted accounting methods. Our analysis shows that clinical trials comprise the largest portion of overall therapeutic complex medical device development costs at $32.1 million which accounts for around 59 percent of R&D expenditures.[2]

The strategy with the largest expected impact on overall therapeutic complex medical device development costs is Simplified Clinical Trial Protocols and Reduced Amendments (-33.4 percent), followed by Improvements in FDA Review Efficiency and Interactions (-22.4 percent) and use of Adaptive Design in clinical study designs (-18.0 percent). Those strategies with the lowest expected development cost savings include use of Electronic Health Records (-2.9 percent), Reduced SDV (-6.0 percent), and use of Standardized Contracts (-8.3 percent).

[2] The model details and key findings regarding development costs are also available at Sertkaya, et al. (2022).

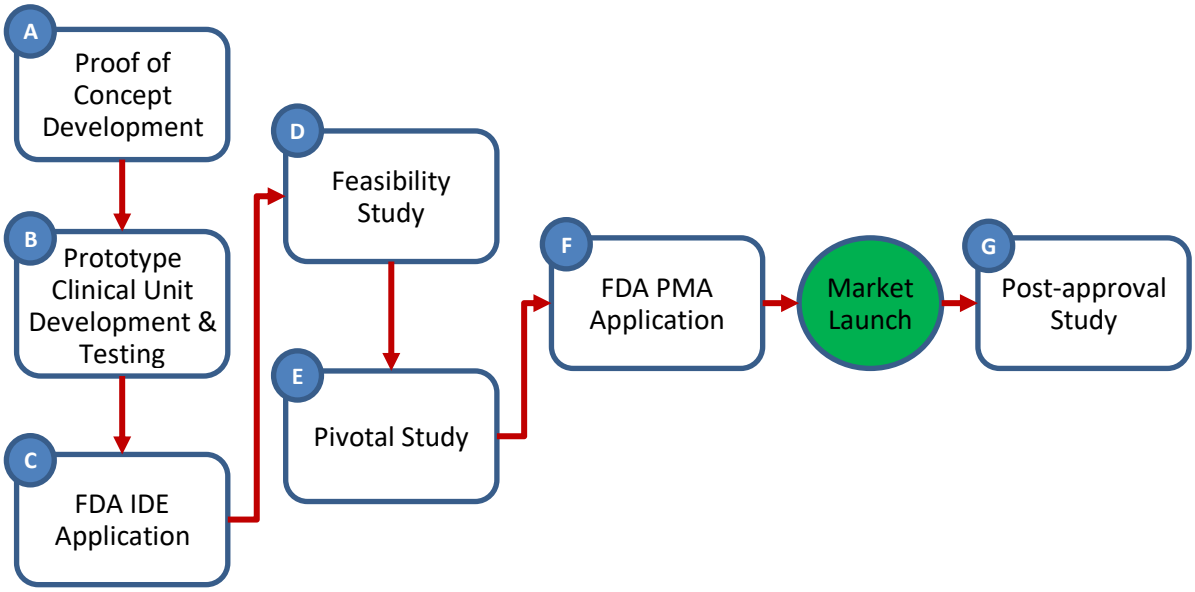
1 INTRODUCTION

There is ongoing debate on how to spur innovation of new medical products while controlling health care costs. Part of this debate has focused on the rising costs of bringing a medical product to market. The medical product development process is complex and clinical studies are the principal method for collecting safety and efficacy data to inform the approval of medical products sold in the U.S., including drugs and medical devices. In 2016, US spending on medical devices and in-vitro diagnostics totaled $173.1 billion, or 5.2 percent of total national health expenditures, making the U.S. the world's largest market for medical devices (Donahoe, 2018). While there have been recent efforts to quantify the total cost of bringing new drugs to the US market (DiMasi, et al., 2016; Wouters, et al., 2020), limited work has been done to estimate the investment needed to bring a new medical device to the US market.

Given that medical devices range from simple tongue depressors to highly complex implantable closed-loop insulin delivery systems, the focus of this study is novel therapeutic complex medical devices (CMDs), a smaller subset. Therapeutic CMDs are Class III devices (e.g., implantable cardiac pacemakers, breast implants, and hemodialysis machines) that usually sustain or support life, are implanted, or present potential unreasonable risk of illness or injury and require the submission of a premarket approval (PMA) application to FDA (U.S. Food and Drug Administration, 2018d). By definition, this study excludes diagnostic devices that are subject to PMA application requirements for marketing in the U.S. from this analysis and those devices that qualify for the FDA 510(k) clearance route.

Figure 1 shows the stages involved in developing a therapeutic CMD from proof of concept (A) through post-marketing activities (G) (U.S. Food and Drug Administration, 2011; Makower, et al., 2010). There are three non-clinical stages that precede testing of the device in humans. The initial stage of development involves the creation of a "proof of concept" document for a medical need that outlines the steps needed to determine whether or not the concept is practical (A—Proof of concept development) (U.S. Food and Drug Administration, 2018e). The next stage involves building the clinical unit (i.e., the device prototype) for bench and animal testing (B—Prototype clinical unit development and testing). Often times, the sponsor holds discussions with the FDA under one or more pre-submissions aka Q-submissions, during this stage. Upon successful completion of the prototype, the sponsor submits an investigational device exemption (IDE) application to FDA to begin clinical studies in human subjects (C—FDA IDE application) (21 CFR 812). As part of the IDE submission, the sponsor submits the investigational plan and report of prior investigations (21 CFR 812) as well as additional relevant information as per 21 CFR and applicable good clinical practice requirements (21 CFR 50 and 21 CFR 56) to the FDA. Additionally, the sponsor also submits relevant documents, such as the investigational protocol and informed consent, to the Institutional Review Board (IRB) designated for the study for review and approval.

Figure 1. Overview of Therapeutic Complex Medical Device Development



Following FDA approval of the IDE and IRB approval, the sponsor can begin the clinical stage, which includes conducting a feasibility study[3] (D—Feasibility study) and a pivotal study (E—Pivotal study). The feasibility study (also referred to as a first-in-human study or a pilot study) is carried out on a small population of patients with the disease or condition to obtain preliminary safety and performance information on the investigational therapeutic CMD. In some cases, more than one feasibility study might be needed. If the feasibility study results are favorable, the sponsor then undertakes a pivotal study on a larger population of patients to determine the safety and effectiveness of the investigational therapeutic CMD as well as the associated adverse events. Similarly, more than one pivotal study may be needed for some therapeutic CMD PMA applications.

Upon successful completion of the pivotal study, the sponsor compiles all the scientific evidence collected with the clinical studies to demonstrate reasonable assurance of safety and effectiveness of the device when used in accordance with the indications for use and submits a PMA application to FDA for review and approval (F—FDA PMA application). The sponsor can begin marketing its device in the U.S. if the PMA application is approved. FDA may require sponsors to conduct one or more post-approval studies to answer additional safety and effectiveness questions related to the device post market (G—Post-approval study).

According to one study, the development cost (from concept to approval) for a complex medical device that requires a Premarket Application (PMA) submission is $94 million with the clinical trial stage (stages D—Feasibility study and E—Pivotal study in Figure 1) comprising 51 percent ($47.9 million) of that total (Makower, et al., 2010). Lowering these development costs

[3] In some cases, the sponsor may choose to conduct a pivotal study without undertaking a feasibility study first. This is common when the device for which an approval is sought for is the n^{th} version of an existing device or the goal is to obtain an expansion of the indication(s) for the existing device.

can encourage more companies to undertake therapeutic CMD development. In a previous study, we identified several promising strategies with potential to improve medical device development efficiency and hence reduce costs (Eastern Research Group, Inc., 2022). These strategies included:

- **Mobile technologies—**Mobile technologies can include cell phones, wearable trackers, and other devices that capture data directly from patients. Electronic data capture means capturing study data in electronic format. The strategy could entail encouraging the use of mobile and other technologies in clinical trials and the development process as a whole and clarifying requirements around their use.

- **Simplified clinical trial protocols and reduced amendments—**The strategy could entail encouraging sponsors to simplify clinical trial protocols, where possible, ensuring that they have a clear understanding of what is required by FDA and what is superfluous.

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- **Biomarkers as surrogate endpoints—**Biomarkers as surrogate endpoints are biological indicators that may correlate with the desired clinical endpoint, for example when it would take a long time for the clinical endpoint to become evident. The strategy could entail clarifying the path to biomarker validation or encouraging collaboration between academics, public entities, and industry to develop and validate biomarkers for use as surrogate endpoints.

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2 STUDY OBJECTIVE

The primary aim of this study is to evaluate the potential savings from implementing the strategies identified above. To facilitate this evaluation, an analytical model that accounts for the cost, duration, the probability of successfully transitioning from one development stage to the next depicted in Figure 1 is needed. Thus, our secondary objective is the development of such a model using public and private data sources.

3 ANALYTICAL FRAMEWORK

To be able to assess the impact of clinical trial strategies discussed in Section 1 above on development costs, we first need estimates of baseline development costs for therapeutic

[4] FDA issued regulations and guidance on the use of centralized IRBs in multi-institutional drug studies back in 2006. Additionally, in 2016, the 21st Century Cures Act removed the requirement for review by "local" IRB for device studies, thereby making it possible to use centralized IRBs in medical device trials. While the use of centralized IRBs has gained widespread adoption in drug development programs, their use in medical device trials remains low.

CMDs. We use the method by DiMasi et al. (2016; 1991) that takes account of the cost of failures and cost of capital. The methodology is described in detail in DiMasi et al. (1991); thus, we only summarize it below.

As shown in Figure 1, therapeutic complex medical device development progresses in phases from early research and development to animal testing, to testing in humans, to regulatory submission for marketing approval and to post-approval studies. If the cash outlay (also known as out-of-pocket cost) associated with a given phase i is C_i, then the expected cost, $E(C_i)$, that incorporates failures can be computed by dividing this cost by the transition success probability from phase i to launch, p_i, i.e.,

$$E(C_i) = \frac{C_i}{p_i}$$

Assuming that phase costs are distributed uniformly over the length of the phase, t_i, the capitalized cost, CC_i, that accounts for the opportunity cost of the investment in the therapeutic CMD is given by:

$$CC_i = \int_{t_{i,e}}^{t_{i,b}} \left(\frac{C_i}{t_i}\right)(e^{rt})\,\mathrm{d}t$$

where r is the cost of capital that captures the time value effect; $t_{i,b}$ is the time from the beginning, b, of the given phase to product launch, and $t_{i,e}$ is the time from the end, e, of the given phase to product launch. The above equation then becomes:

$$CC_i = \frac{\left(C_i / t_i\right)}{r}\left(e^{rt_{i,b}} - e^{rt_{i,e}}\right)$$

Given the above equations, we can then compute the expected capitalized cost of phase i that accounts for the cost of failures as well as the cost of capital as:

$$E(CC_i) = \frac{CC_i}{p_i}$$

Then the total expected capitalized cost of development for a therapeutic CMD, $E(CC)$, is the sum of the expected capitalized cost of each phase i,

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

where i = non-clinical, feasibility study, pivotal study, FDA review, and post-approval study.

For example, suppose the total out of pocket cash outlay for a feasibility study is $5 million for a given therapeutic CMD x and the probability of that product making it to market

given that it is in the feasibility study phase is 40 percent, then the expected cost of the feasibility study stage, $E(C_2)$, that accounts for failures is $12.5 million, i.e.,

$$E(C_2) = \frac{C_2}{p_2} = \frac{\$5{,}000{,}000}{0.40} = \$12{,}500{,}000$$

If we further assume that the cost of capital, r, is 1 percent per month (i.e., 12 percent per annum) and that the feasibility study phase lasts 35 months (t_2 = 35) begins 105 months before product launch (t_2^b=105) and ends 71 months before product launch (t_2^e=71) then the capitalized cost of the feasibility study phase, CC_2, that accounts for the opportunity cost of the investment in product x is $11.8 million, i.e.,

$$CC_2 = \frac{\left(C_2 / t_2\right)}{r}\left(e^{rt_{2,b}} - e^{rt_{2,e}}\right) = \frac{\left(\$5{,}000{,}000 / 35\right)}{0.01}\left(e^{0.01x105} - e^{0.01x71}\right) = \$11{,}766{,}569$$

Using the above equations, we can compute the expected capitalized cost of the feasibility study phase, $E(CC_2)$, as $29.4 million:

$$E(CC_2) = \frac{CC_2}{p_2} = \frac{\$11{,}766{,}569}{0.40} = \$29{,}416{,}423$$

We use this approach to compute the total expected capitalized cost of developing a therapeutic CMD as described in sections below.

4 DATA SOURCES

4.1 CLINICALTRIALS.GOV DATA

Clinicaltrials.gov is a registry launched in September 2000 to provide protocol and results information on clinical trials conducted in the U.S. and around the world. Clinicaltrials.gov data are updated daily and provide information on such parameters as study start and end dates and number of patients enrolled for the registered studies that are relevant for modeling. We used a snapshot of the clinicaltrials.gov data downloaded on October 30, 2018 (i.e., the monthly archived data file titled, "20181001_pip-delimited-export.zip") through the Clinical Trials Transformation Initiative's (CTTI) Access to Aggregate Content of ClinicalTrials.gov (AACT) initiative for this analysis.

As of October 30, 2018, when this part of the study was conducted, the database contained 285,680 unique research studies. Of these studies, a total of 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,[5] we

[5] Some of the medical device clinical trials are conducted for research purposes only. We judged that those studies where the funder type is "NIH," "Other U.S. Federal Agency," or "All Others (Individuals, Universities, Organizations)" are likely to fall under this category and be out of scope for our study.

limited our sample to those 12,271 studies that have at least one sponsor listed as "industry." We then used this subset of 12,271 studies to define our feasibility, pivotal, and post-approval study samples as described below.

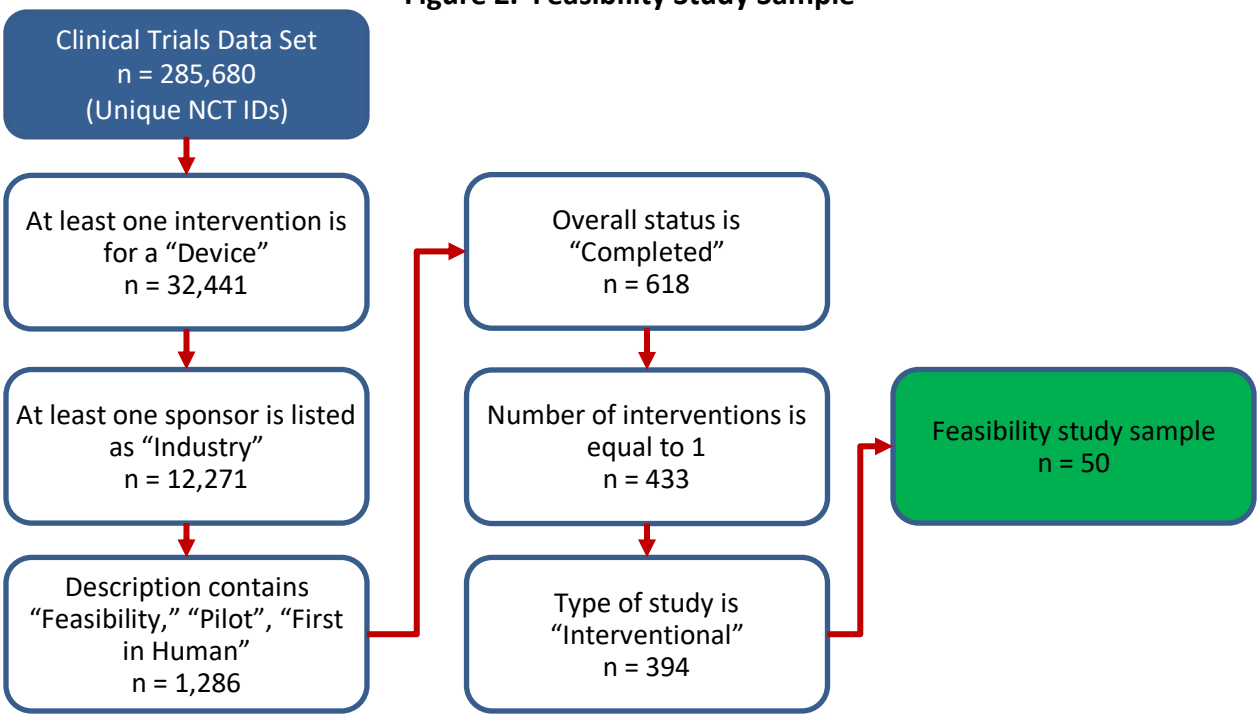
In order to create these three samples, we evaluated the utility of various data fields found in the clinicaltrials.gov database to characterize the development stage of the 12,271 selected studies. While several of these fields appeared relevant for this purpose (e.g., study type, overall status), many contained missing data or appeared to include incorrect classifications. For example, the clinicaltrials.gov database includes a field that identifies the "primary purpose" of each intervention study, with one of the responses being "device feasibility". While certainly relevant to the needs of this project, this field was blank for numerous studies and in some cases, seemed to be coded incorrectly. We were able to evaluate this by comparing classifications to those in the FDA PMA Approvals Database—which we assume are less prone to misclassification error for a small subset of studies. The results of this investigation showed that several studies identified as feasibility studies in the FDA PMA Approvals Database were coded with a primary purpose of "treatment" rather than "device feasibility" as should be in the clinicaltrials.gov database. As another example, the database includes a field for the study phase, with an entry of "NA" indicating that the "trial is without phases (for example, studies of devices or behavioral interventions)." Several of the pivotal studies identified in the FDA PMA Approvals Database were flagged with a phase of "NA", while some of the identified feasibility studies were coded with "Phase 2." Both of these examples highlight the potential for misclassification within certain fields due to missing data and/or reporting errors.

Due to these limitations, we were not able to conduct rigorous statistical analyses using the clinicaltrials.gov database. We were, however, able to use the database to identify a small convenience sample for each of three study categories by relying on data fields that are mostly complete and likely coded correctly (e.g., study status, study type [observational or interventional], sponsor, intervention type), and manually reviewing individual study titles and descriptions. Additional details on this process for feasibility studies, pivotal studies, and post-approval studies are provided in Section 4.1.1, Section 4.1.2, and Section 4.1.3, respectively. We used the information from these studies to estimate some of the key input parameters for our model (e.g., average study enrollment, average study duration).

4.1.1 Feasibility Study Sample

Of the 12,271 industry-sponsored device trials deemed in-scope, 1,286 contained "feasibility," "pilot," or "first in human" in their title, official title, brief description, or detailed description fields. These represent *potential* feasibility studies. To identify *actual* medical device feasibility studies among the potential feasibility studies, we further reduced this dataset to only those that were completed (618 studies), listed only one intervention (433 studies), and specified the type of study as being interventional (394 studies) (see Figure 2).

Figure 2. Feasibility Study Sample

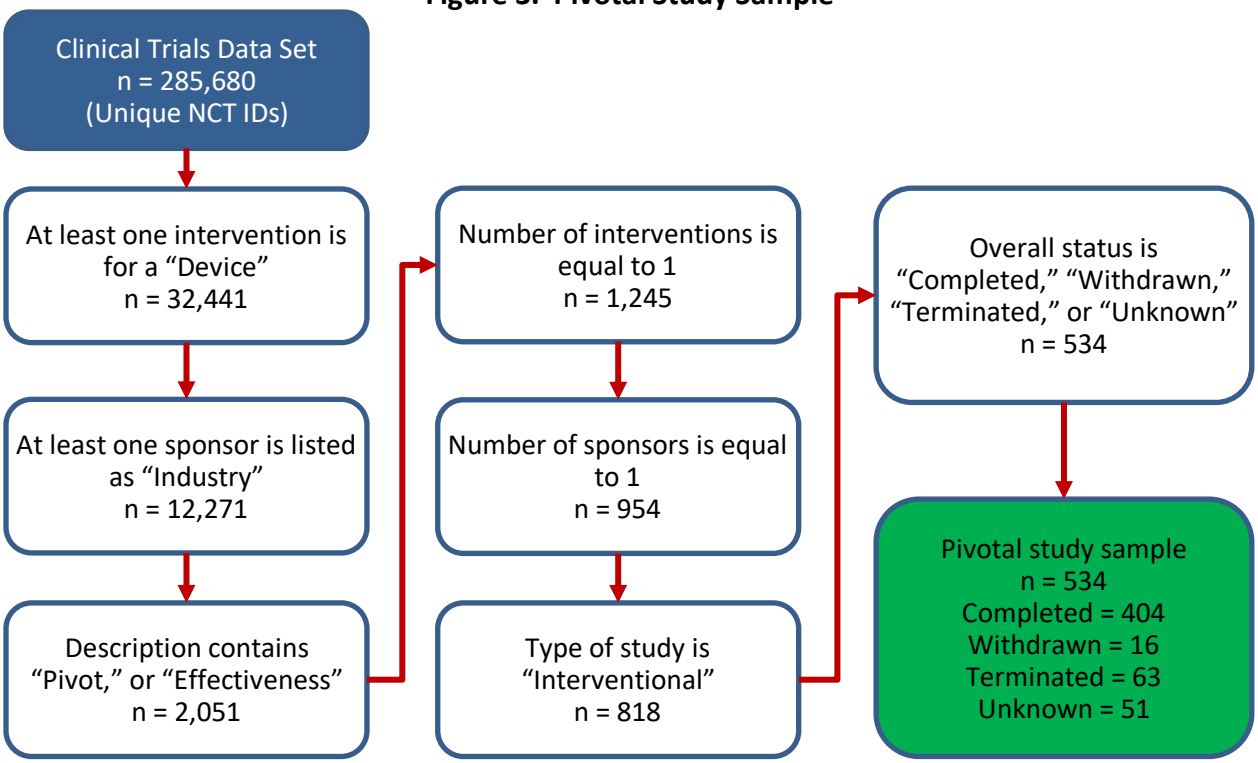


Next, we reviewed the detailed descriptions of the remaining 394 studies manually. Based on this review, we were able to identify 50 out of the 394 studies as being medical device feasibility studies. We were, however, unable to ascertain whether the remaining 344 studies were in fact medical device feasibility studies based on our review of the information available for each study. Thus, these 50 studies that we could be reasonably sure were, in fact, feasibility studies constitute our feasibility study convenience sample.

4.1.2 Pivotal Study Sample

Of the 12,271 industry-sponsored device trials in our sample, 2,051 contained "pivot" or "effectiveness" in their title, official title, brief description, or detailed description fields. These represent *potential* pivotal studies. As was done for the feasibility study sample, we further reduced the dataset to those that listed only one intervention (1,245 studies), had a single sponsor (954 studies), specified the type of study as being interventional (818 studies), and had an overall status designation of "completed," "withdrawn," "terminated," or "unknown" (see Figure 3).

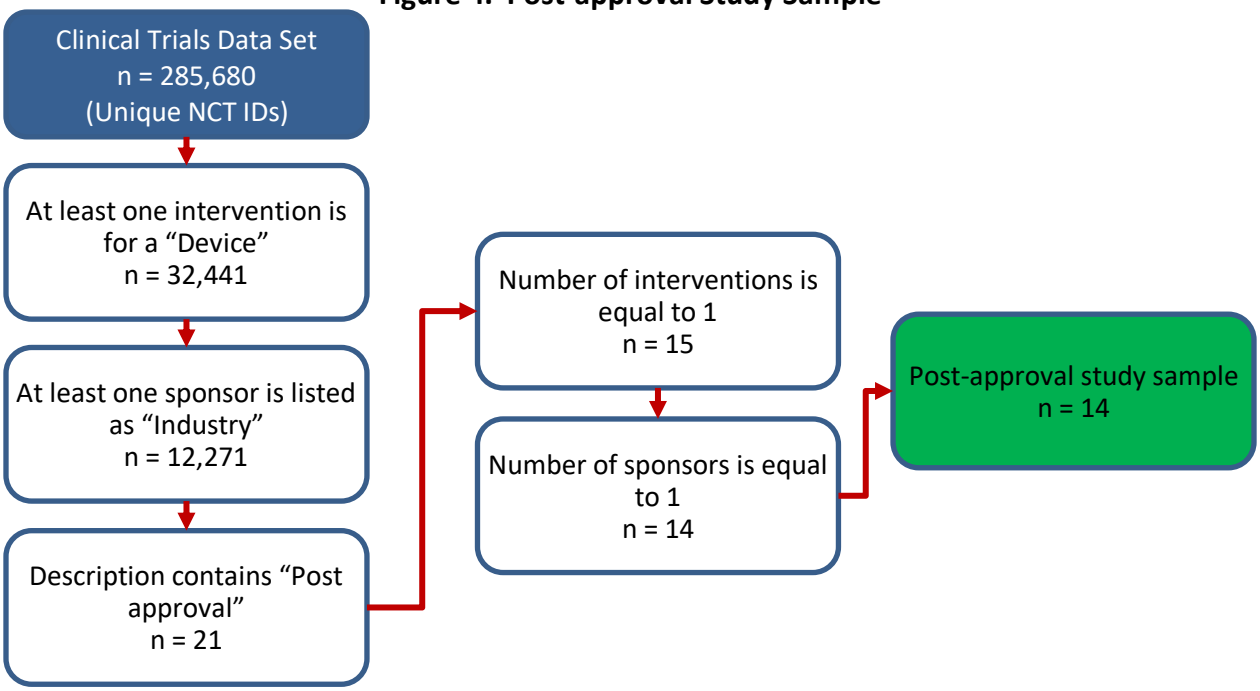
Figure 3. Pivotal Study Sample



4.1.3 Post-approval Study Sample

Of the 12,271 industry-sponsored device trials in our sample, 21 contained "post approval" in their title, official title, brief description, or detailed description fields. These represent *potential* post approval studies. We further reduced this dataset to only those that listed one intervention (15 studies) and had a single sponsor (14 studies) (see Figure 4).

Figure 4. Post-approval Study Sample



4.2 FDA DATABASES

FDA makes PMA approval as well as post-approval study data available to the public through the FDA website (U.S. Food and Drug Administration, 2018f; U.S. Food and Drug Administration, 2018g).

4.2.1 PMA Approvals Database

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 (SSED) attachment, and product labeling among other fields. Table 1 below provides a summary of the data we downloaded from this database on September 7, 2018 covering the period from January 2013 through September 2018.

Table 1. Summary Information on FDA PMA Approvals, January 2013 through September 2018

Data Element	Count
Total Number of Original PMAs	191
Diagnostic Devices	40
Therapeutic Devices	151
Implantable Device	89
Life-Sustain/Support Device	28
With Feasibility Study Information in the SSED	19
With Pivotal Study Information in the SSED	149

4.2.2 Post-approval Study (PAS) Database

FDA requires manufacturers of certain high-risk devices to conduct post-approval studies (PASs) to provide additional safety and effectiveness data. Data obtained from these PASs supplement performance data contained in PMA and possibly uncover design, mechanical, electrical, and user related problems not identified in pre-market clinical testing. Additionally, these data are also useful for reducing residual uncertainty from the premarket clinical data, confirming performance with longer term outcomes and in real world settings. All Class III devices are potentially subject to post-approval studies. As per 21 CFR 860(c)(3), a device is classified as Class III "if insufficient information exists to determine that general controls are sufficient to provide reasonable assurance of its safety and effectiveness or that application of special controls … would provide such assurance and if, in addition, the device is life-supporting or life-sustaining, or for a use which is of substantial importance in preventing impairment of human health, or if the device presents a potential unreasonable risk of illness or injury."[6]

Ideally, the outline of the PAS is agreed on by the FDA and the sponsor as part of the PMA review and before the PMA decision letter is issued to the sponsor. Designated manufacturers then submit a PAS study protocol within 30 days of PMA approval and begin the PAS upon FDA approval of the protocol.[7] The requirement does not stipulate a PAS protocol that manufacturers must follow, although manufacturers must prove to FDA that the study design is scientifically sound.

Post-approval studies associated with approved devices are publicly available on the FDA website. The PAS database provides information on study status (e.g., ongoing, completed, adequate progress) and study protocol parameters, such as number of patients planned, number of patients enrolled, study design (e.g., prospective, retrospective, randomized clinical trial), type of data source (e.g., new, external or sponsor registry), and type of analysis (descriptive versus analytical), among others. Further, the database links each PAS to an approved device by PMA number. As of April 23, 2019 (date of data download), the database contained a total of 718 PASs (see Table 2).

Of these, 322 PASs were for devices approved during the 2013 – 2018 period. Of the 322 PASs, 139 PASs corresponded to 85 out of the 151 therapeutic device PMAs selected (see Table 1) for inclusion in this study. However, only 109 out of these 139 PASs corresponding to 73 PMAs required new data collection by the sponsor (i.e., the data source in the publicly available FDA PAS database indicated "New Data Collection" for the Data Source variable). The

[6] All permanent implants that FDA identifies as subject to tracking also are subject to PAS requirements. Additionally, FDA may impose post-approval requirements, including continued evaluation of a device (i.e., a PAS study), in a PMA approval, by regulation at the time of approval of the PMA, or by regulation subsequent to approval for devices that pose additional questions of safety and effectiveness left unanswered by the PMA process (21 CFR 814.82). These "discretionary" devices subject to PAS requirements are, however, relatively few compared to the categories listed.

[7] In some cases, the entire PAS protocol is developed and agreed to during the PMA review process. When the PMA decision letter contains the outline of the PAS, that outline specifically calls out key requirements that must be met (e.g., study size, duration, endpoints, etc.).

average number of PASs requiring new data collection for those PMAs required to conduct a PAS by FDA was 1.5.

Table 2. Summary Information on FDA Post-approval Studies for Medical Devices

Data Element	Count
Total Number of PASs	718
Number of PASs for During 2013-2018 Period	322
Humanitarian Device Exemption (HDE) Application Related	12
PMA related	310
Corresponding to the 151 PMAs in Our Approved PMA Sample (see Table 1) [a]	139
External Registry	10
Sponsor Registry	14
Other Data Source	1
NA	5
New Data Collection	109

NA = Not available
[a] Excludes two bench/lab studies.

4.3 MEDIDATA SOLUTIONS DATA

We used a custom tabulation from three proprietary databases on clinical trial costs, which are offered by Medidata Solutions:[8]

- Medidata Grants Manager® (PICAS® database) – PICAS provides industry-wide negotiated site cost information. It is a database of negotiated investigator grants—it includes more than 250,000 grants and contracts and 27,000 protocols in over 1,400 indications—that provides benchmarked costs typically used for clinical trial budget planning.

- Medidata CRO Contractor® (CROCAS® database) – The CROCAS database contains thousands of negotiated outsourcing contracts. It includes comprehensive data from CRO contracts—detailed across such dimensions as therapeutic area, phase, and geography.

- Medidata Insights™ – Medidata Insights is the turnkey clinical analytics solution that provides advanced visualization of clinical operational performance metrics alongside company and industry benchmarks. The Insights metrics warehouse is comprised of data from more than 7,000 studies gathered seamlessly from over 120 clinical trial sponsors.

The data tabulation, referred to as Medidata hereinafter, covered the period 2004 through 2012 and included average expenditures for the full range of cost elements associated

[8] Medidata databases contain numerous data elements derived from actual negotiated contracts, and these resources are widely used by medical device companies, contract research organizations (CROs), and academic researchers to identify prevailing rates for trial planning, budget development, and grant negotiation (Medidata Solutions, 2012).

with clinical trials, including cost of IRB approvals, cost of protocols, patient recruitment costs, and administrative staff costs among others by therapeutic area.[9] Devices and Diagnostics was one of the reported therapeutic areas which is what we used to estimate per-patient clinical study costs for therapeutic CMDs.

5 MODEL PARAMETERS AND ASSUMPTIONS

Table 3 presents the parameter estimates and assumptions for our therapeutic CMD development cost model. The following sections discuss the basis for these estimates.

5.1 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 also estimate that the parameter has a triangular distribution in which 60 months represents the most likely value, 36 months the minimum and 108 months the maximum for highly complex implantable devices based on our follow-up discussions with medical device experts.

We derived our feasibility study phase estimate of 28 months by combining the 50 feasibility studies from our clinicaltrials.gov sample (see Section 4.1.1) with the 29 feasibility studies from our FDA PMA approvals database sample (see Section 4.2.1), removing the duplicate studies (one study), and taking the average feasibility study duration from the combined sample. Our pivotal and FDA 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 (see Section 4.1.3). 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.

5.2 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.

[9] More information on the data along with assumptions used to extrapolate certain variables are available in (Sertkaya, et al., 2016).

Table 3. 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	Combined clinicaltrials.gov feasibility study and FDA PMA approval samples
	Pivotal Study	56.9	FDA PMA approval sample
	FDA 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 Review	42.4	FDA PMA approval sample
	FDA Review to Approval	17.4	FDA PMA approval sample
Number of Patients Enrolled	Non-clinical	NA	Not applicable
	Feasibility Study	42	Combined clinicaltrials.gov feasibility study and FDA PMA approval samples
	Pivotal Study	565	FDA PMA approval sample
	FDA 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 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 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 Review	75.7%	Clinicaltrials.gov pivotal study sample
	FDA Review to Approval	80.5%	U.S. Food and Drug Administration, (2018i)
Cost of Capital (%)		10.4%	Harrington (2012)

For the feasibility study phase to pivotal study phase estimate of 37.2 months, we used the clinicaltrials.gov feasibility study sample described in Section 4.1.1. 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 (see Section 4.1.2). 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 (see Table 1).[10] 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 (see Table 1) 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).

5.3 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 (see Section 4.1.1) and FDA PMA approval samples (see Section 4.2.1). Next, we estimated that on average, a sponsor conducts 1.53 feasibility studies per PMA based on the 19 PMAs (see Table 1) that provided information on the feasibility studies conducted in their SSEIs. This translated to an estimate of 42 patients ($\cong 27.47 \times 1.53$) 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 sponsor conducts 1.40 pivotal studies per PMA based on the 149 PMAs (see Table 1) that provided information on the pivotal studies conducted in their SSEIs. This translated to an estimate of 565 patients ($\cong 402.47 \times 1.40$) for the pivotal study phase.

[10] 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 (see Table 1), 79 percent reported one pivotal study, 13 percent reported two, and the remaining 8 percent reported three or more pivotal studies in their SSEIs.

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 (see Section 4.2.2). 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,[11] we estimated the average number of patients for the post-approval study phase at 414 (≅ 895 × 0.46).

5.4 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.

From Table 4, 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.

Table 4. Per-patient Costs for the "Devices and Diagnostics" Therapeutic Area Reported by Medidata Solutions

Medidata Solutions Reported Phase	Mean (in 2012 $)	Mean (in 2018 $) [a]	Matched Medical Device Study Phase	Mean (in 2018 $)
Phase 1	$29,463	$34,059	Feasibility Study	$34,059
Phase 2	$59,510	$68,793	Pivotal Study [b]	$54,332
Phase 3	$34,490	$39,870		
Phase 4	$12,471	$14,416	Post-approval Study	$14,416

[a] The 2012 $ figures are adjusted to year 2018 by using Consumer Price Index for All Urban Consumers: Medical Care, Index 1982-1984=100, Monthly, Seasonally Adjusted table published by the U.S. Bureau of Labor Statistics.
[b] The value represents the average of Phase 2 and Phase 3 per-patient costs reported by Medidata Solutions.

5.5 OUT-OF-POCKET COSTS BY STAGE OF DEVELOPMENT

The out-of-pocket cost parameter represents the average out-of-pocket expenses (not adjusted for failures or cost of capital) a sponsor 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 (Eastern Research Group, Inc., 2022) coupled with focused follow-up interviews we conducted with medical device experts to estimate the out-of-pocket costs for

[11] 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).

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. Thus, we assumed that this parameter follows a triangular distribution in which $20 million represents the most likely value, $15 million the minimum and $35 million the maximum in our analysis.

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[12]) 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,[13] respectively.

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, 2018h). Inflating these 2014 figures to 2018 dollars, we estimated the out-of-pocket costs for the FDA review phase at around $1.9 million.

5.6 PHASE TRANSITION SUCCESS PROBABILITIES

The phase transition success probability parameter represents the probability of a sponsor 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 (Eastern Research Group, Inc., 2022) 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

[12] 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).

[13] 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.

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.

As discussed in Section 5.2 above, 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 review phase, we again relied on clinicaltrials.gov data, but employed a different methodology. As described in Section 4.1.2, 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 review 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, 2018i). MDUFA quarterly updates report the percent of original PMAs approved by CDRH from 2001 to August 2018 annually (see Table 5). We used the historical average of 80.5 percent (with a median of 82 percent) to represent the FDA submission to approval probability.

Table 5. 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%

Year	Percent of Original PMAs Approved [a]
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.

5.7 OPPORTUNITY COST OF CAPITAL

The opportunity cost of capital (OCOC) represents the rate of return (net of inflation) that the sponsor would otherwise be able to earn at the same risk level as the investment in the new drug that has been selected. Some critics have argued that "innovative companies must do R&D, and this is a regular cost of doing business; so estimated profits foregone should not be added to out-of-pocket costs. If revenues are coming in from other products, then the [R&D] costs are recovered as one goes along" (Light & Warburton, 2011). Others have questioned whether the appropriate cost of capital should be as high as 11 percent, the value used in several studies from the Tufts Center for the Study of Drug Development (Tufts CSDD).

As described by Chit, et al. (2015), there is an opportunity cost associated with the use of capital, which is a scarce resource, and this cost needs to be accounted for in estimating development costs. The value of OCOC can vary significantly by sponsor-specific factors, such as product portfolio, venture capital funding, and size of company, as well as other exogenous factors, such as economic and regulatory climate for drug development projects. There are accepted methods in finance for estimating the opportunity cost of capital for different economic sectors and firms, including the capital asset pricing model (CAPM), and the Fama and French (F-F) 3-factor model. The CAPM model is the most widely used approach (Chit, et al., 2015). There are numerous CAPM studies that evaluated OCOC for the biopharmaceutical market as a whole as well as some broad sub-sectors, such as small and large molecules. According to a study by Harrington (2012), the estimated OCOC 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 COC (see Table 6).

Table 6. Opportunity Cost of Capital (OCOC) Estimates from Harrington (2012)

Estimation Method	Firm Size	Study Period	Sample Size	Opportunity Cost of Capital (OCOC) Net of Inflation
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%

Estimation Method	Firm Size	Study Period	Sample Size	Opportunity Cost of Capital (OCOC) Net of Inflation
			Average	**10.4%**

[a] CAPM = Capital asset pricing model

6 RESULTS

6.1 BASELINE DEVELOPMENT COST ESTIMATES

According to a 2010 study by Makower et al. (2010), the average out-of-pocket cost of developing a medical device that requires a PMA application to FDA is around $118.5 million in 2018 dollars (Table 7). Of these costs, around 30 percent is non-clinical stage related, 50 percent is clinical stage related and the remaining 20 percent is for getting FDA PMA approval for marketing the device in the U.S. The study does not provide costs associated with any post-approval studies developers may need to conduct after obtaining PMA approval. Further, the estimates reported in the study are based on a survey of 204 small medical device companies in the U.S.

Table 7. Average Time and Expenditures by Stage of Development for a PMA Product Reported in Makower et al. (2010)

Stage		Duration (in Months) [a]		Total Expenditures (in 2010 $ Million) [b]		Total Expenditures (in $ 2018 Million) [c]	
		Value	%	Value	%	Value	%
Non-clinical	Concept Development and Proof-of-concept	31.0	26%	$10.0	10%	$12.3	10%
	Clinical Unit Development	17.5	15%	$8.0	8%	$9.9	8%
	Process of Obtaining IDE	14.0	12%	$11.0	11%	$13.6	11%
Clinical	Safety/feasibility Clinical Study	13.5	11%	$8.0	8%	$9.9	8%
	Pivotal Clinical Study	27.5	23%	$41.0	43%	$50.6	43%
FDA PMA	Process of Obtaining PMA	17.0	14%	$18.0	19%	$22.2	19%
Total		**120.5**	**100%**	**$96.0**	**100%**	**$118.5**	**100%**

[a] Based on Figure 11 in Makower, et al. (2010)
[b] Based on Figure 13 in Makower, et al. (2010)
[c] The figures are adjusted using the Consumer Price Index for All Urban Consumers: Medical Care, Index 1982-1984=100, Monthly, Seasonally Adjusted table reported by Federal Reserve Bank of St. Louis (2019).

Our analysis suggests that the average out-of-pocket cost of developing a therapeutic CMD is around $54 million before conducting post-approval studies, and approximately $60 million when post-approval studies are accounted for (see Table 8).

Of those costs exclusive of post-approval studies, 37 percent is non-clinical stage related, 60 percent is clinical stage (i.e., feasibility and pivotal study) related, and the remaining 3 percent is associated with the FDA review phase. When capitalized to account for the time value of money and after accounting for the costs of failures, expected capitalized average

development cost for therapeutic CMD development is approximately $522 million before conducting post-approval studies and $526 million after conducting them. As indicated, capitalized costs are higher than out-of-pocket costs because they take into account the opportunity cost of capital that embodies the time value of money as well as the fact that there will be failures along the way. These figures represent our baseline cost of therapeutic CMD development against which we evaluate different strategies designed to improve likelihood of success and/or reduce non-clinical, clinical, and FDA PMA phase related costs and durations.

As Table 8 illustrates, the primary driver of development cost is non-clinical stage expenditures when we account for cost of failures and opportunity cost of capital. From a capitalized out-of-pocket cost perspective that takes account of the time value of the investment but not failure costs, non-clinical development stage accounts for nearly 60 percent of total capitalized development costs, whether or not post-approval costs are included.

From an expected capitalized cost perspective in which both cost of failures and the time value of the investment are incorporated, the share of total expected development cost represented by the non-clinical stage is around 85 percent, whether or not post-approval costs are included. Non-clinical stage represents the largest portion of total expected capitalized development costs primarily because the probability of moving from non-clinical stage to a marketable therapeutic PMA device is only 13.7 percent.[14] Thus, the $20 million and 5 years needed to conduct preclinical testing are much greater in real economic impact than their nominal value suggests. As the developer successfully transitions from one development stage to another, the likelihood of approval hence expected returns change. 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, and obtaining an FDA IDE to begin human trials), the odds of a device making it to market is significantly higher (61 percent) if the device has already cleared the non-clinical and feasibility study stages than one that is at the proof-of-concept development stage (14 percent).

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. Pivotal clinical stage represents the vast 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 $30.7 million vs. $1.4 million).

[14] Multiplying together all the phase transition success probabilities listed in Table 3 (i.e., successfully moving from non-clinical phase to FDA marketing approval), results in a product of 13.7 percent.

Table 8. Average Cost of Developing a Therapeutic Complex Medical Device for the U.S. Market (in Million $ 2018)

Phase	Transition Success Probability [a]	Out-of-Pocket Costs (in $ 2018) [b]		Expected Out-of-Pocket Costs (in $ 2018) [c]		Capitalized Out-of-pocket Costs to Date of Launch (in $ 2018) [d]		Expected Capitalized Out-of-pocket Costs (in $ 2018) [e]	
		$	%	$	%	$	%	$	%
Non-clinical	13.7%	$20,000,000	37%	$145,736,577	72%	$60,768,477	57%	$442,809,494	85%
Clinical (Feasibility and Pivotal Phases)	NA	$32,100,901	59%	$55,249,133	27%	$43,586,656	41%	$76,792,806	15%
Feasibility Study	29.2%	$1,428,249	3%	$4,885,698	2%	$2,937,394	3%	$10,048,123	2%
Pivotal Study	60.9%	$30,672,652	57%	$50,363,435	25%	$40,649,262	38%	$66,744,683	13%
FDA Review	80.5%	$1,852,816	3%	$2,301,634	1%	$1,999,486	2%	$2,483,834	0%
Post-approval Study [f]	NA	$5,961,197	NA	$5,961,197	NA	$4,280,024	NA	$4,280,024	NA
Total (without post-approval study costs)	**NA**	**$53,953,717**	**100%**	**$203,287,345**	**100%**	**$106,354,619**	**100%**	**$522,086,135**	**100%**
Total (with post-approval study costs)	**NA**	**$59,914,914**	**NA**	**$209,248,542**	**NA**	**$110,634,644**	**NA**	**$526,366,159**	**NA**

NA = Not applicable

Figures may not add up due to rounding.

[a] The figure represents the transition probability from the given stage to approval.

[b] These are the raw out-of-pocket expenses not adjusted for opportunity cost of capital or failures.

[c] The 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 time value of the investment.

[d] The figures represent the out-of-pocket costs at the point of launch after adjusting for the time value of the investment; computed in accordance with approach described in Section 2. Capitalized out-of-pocket costs take into account the time value of the investment but not the costs of failures.

[e] Expected capitalized costs take into account the costs of failures and the time value of money.

[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.

6.2 IMPACT OF SELECT CLINICAL TRIAL STRATEGIES ON THE TOTAL COST OF THERAPEUTIC COMPLEX MEDICAL DEVICE DEVELOPMENT

As described in our previous study (Eastern Research Group, Inc., 2022), we asked our panel of medical device experts to evaluate the impact of various clinical study strategies on the cost, duration, and phase transition success probability of therapeutic CMD clinical as well as non-clinical, if applicable, stages. A summary of the estimates drawn from the expert panel is presented in Table 9. Negative percentages indicate reductions in a given parameter (e.g., use of standardized contracts would *reduce* clinical study costs, on average, by 2 percent during the clinical development process), and positive percentages indicate increases in a given parameter (e.g., using a staged approval process would *increase* a developer's probability of success, on average, by 3 percent during the clinical development process).

We then evaluated the overall impact of each strategy on total expected development cost (see Table 10). Using our total expected capitalized out-of-pocket cost (including post-approval studies) of $526.4 million as our baseline, we evaluated the change (or delta [Δ]) to this total expected capitalized cost if a developer were to implement each strategy. For each strategy, we evaluated the reduction in overall expected development cost attributable to the cost savings, time savings, and increases in probability of phase transition success associated with that strategy. For example, Simplified Clinical Trial Protocols and Reduced Amendments are associated with developer cost savings of 6.7 percent, time savings of 7.6 percent, and savings due to improvements in the probability of success of 22.6 percent. Combined, these changes result in a total expected development cost of $350.8 million, which is approximately 33.4 percent lower than our baseline estimate of $526.4 million.

From Table 10, the strategy with the largest impact on overall development costs is Simplified Clinical Trial Protocols and Reduced Amendments (33.4 percent), followed by Improvements in FDA Review Efficiency and Interactions (22.4 percent) and use of Adaptive Design in clinical study designs (18.0 percent). Those strategies with the lowest expected development cost savings include use of Electronic Health Records (2.9 percent), Reduced SDV (6.0 percent), and use of Standardized Contracts (8.3 percent).

Table 9. Expert Estimates of Strategy Impacts on Cost, Duration, and Probability of Phase Transition Success for Therapeutic Complex Medical Devices (CMDs)

Strategy	Phase	Cost	Duration	Success Likelihood
Mobile Technologies	Non-clinical	0%	0%	0%
	Feasibility Study	0%	-2%	2%
	Pivotal Study	1%	-5%	4%
	FDA Review	-2%	-2%	2%
	Post-approval	-6%	-2%	NA
Simplified Clinical Trial Protocols and Reduced Amendments	Non-clinical	-5%	-5%	5%
	Feasibility Study	-12%	-12%	9%
	Pivotal Study	-17%	-13%	9%
	FDA Review	-13%	-12%	6%
	Post-approval Study	-8%	-7%	NA
Reduced SDV	Non-clinical	-1%	-1%	0%
	Feasibility Study	-5%	-4%	0%
	Pivotal Study	-10%	-6%	0%
	FDA Review	-4%	-3%	0%
	Post-approval Study	-12%	-9%	NA
Improvements in FDA Review Efficiency and Interactions	Non-clinical	-1%	-4%	9%
	Feasibility Study	-2%	2%	7%
	Pivotal Study	-4%	0%	8%
	FDA Review	-3%	-1%	4%
	Post-approval Study	-6%	-2%	NA
Staged Approval	Non-clinical	0%	0%	0%
	Feasibility Study	-2%	-1%	2%
	Pivotal Study	-7%	-6%	3%
	FDA Review	-4%	-3%	4%
	Post-approval Study	2%	2%	NA
Biomarkers as Surrogate Endpoints	Non-clinical	0%	0%	0%
	Feasibility Study	0%	0%	0%
	Pivotal Study	0%	0%	0%
	FDA Review	0%	0%	0%
	Post-approval Study	0%	0%	NA
Electronic Health Records	Non-clinical	-1%	0%	0%
	Feasibility Study	-1%	-2%	0%
	Pivotal Study	-2%	-3%	0%

Strategy	Phase	Cost	Duration	Success Likelihood
	FDA Review	-2%	-3%	0%
	Post-approval Study	-3%	-3%	NA
Patient Registries	Non-clinical	0%	0%	0%
	Feasibility Study	-4%	-7%	0%
	Pivotal Study	-8%	-10%	3%
	FDA Review	-4%	-5%	3%
	Post-approval Study	-6%	-7%	NA
Adaptive Design	Non-clinical	-2%	-2%	1%
	Feasibility Study	-4%	-4%	4%
	Pivotal Study	-7%	-6%	6%
	FDA Review	-6%	-4%	4%
	Post-approval Study	0%	0%	NA
Standardized Contracts	Non-clinical	0%	0%	0%
	Feasibility Study	-1%	-3%	1%
	Pivotal Study	-2%	-4%	2%
	FDA Review	-2%	-4%	2%
	Post-approval Study	-2%	-4%	NA
Centralized IRBs [a]	Non-clinical	0%	0%	0%
	Feasibility Study	-2%	-4%	0%
	Pivotal Study	-4%	-7%	2%
	FDA Review	-3%	-4%	2%
	Post-approval Study	-4%	-7%	NA
CDC/NIH Developing Epidemiological Data on Disease Incidence [b]	Non-clinical	NA	NA	NA
	Feasibility Study	NA	NA	NA
	Pivotal Study	NA	NA	NA
	FDA Review	NA	NA	NA
	Post-approval Study	NA	NA	NA
Federally-supported cGMP-compliant Manufacturing Facilities [b]	Non-clinical	NA	NA	NA
	Feasibility Study	NA	NA	NA
	Pivotal Study	NA	NA	NA
	FDA Review	NA	NA	NA
	Post-approval Study	NA	NA	NA

Source: Eastern Research Group, Inc., (2022)
NA = Not applicable

The zero percentages represent those cases where an expert indicated that the strategy was not relevant to a particular phase and/or cost, duration, or probability of phase transition success associated with that phase.
[a] Strategy only considered for therapeutic complex medical device development.
[b] Strategy only considered for preventive vaccine development.

Table 10. Estimated Impacts of Strategies on Baseline Cost, Duration, and Phase Transition Success Probability – Therapeutic Complex Medical Devices

Strategy	Change from Baseline due to…							
	Change in Cost		Change in Duration		Change in Success Probability		Total Change [a]	
	$	%	$	%	$	%	$	%
Mobile Technologies	$0.1	0.0%	-$14.5	-2.8%	-$42.2	-8.0%	-$55.5	-10.5%
Simplified Clinical Trial Protocols and Reduced Amendments	-$35.2	-6.7%	-$40.1	-7.6%	-$118.7	-22.6%	-$175.5	-33.4%
Reduced SDV	-$12.7	-2.4%	-$19.0	-3.6%	$0.0	0.0%	-$31.4	-6.0%
Improvements in FDA Review Efficiency and Interactions	-$8.4	-1.6%	$5.1	1.0%	-$115.2	-21.9%	-$118.1	-22.4%
Staged Approval	-$5.0	-1.0%	-$17.9	-3.4%	-$47.4	-9.0%	-$68.2	-13.0%
Biomarkers as Surrogate Endpoints	NE	NE	NE	NE	NE	NE	NE	NE
Electronic Health Records	-$4.4	-0.8%	-$10.8	-2.1%	$0.0	0.0%	-$15.1	-2.9%
Patient Registries	-$6.3	-1.2%	-$31.5	-6.0%	-$33.1	-6.3%	-$68.3	-13.0%
Adaptive Design	-$12.4	-2.4%	-$18.4	-3.5%	-$68.0	-12.9%	-$94.6	-18.0%
Standardized Contracts	-$1.7	-0.3%	-$15.6	-3.0%	-$27.2	-5.2%	-$43.6	-8.3%
Centralized IRBs	-$3.2	-0.6%	-$21.6	-4.1%	-$22.4	-4.3%	-$46.0	-8.7%

NE = Not estimated. Insufficient number of expert responses to estimate impacts.

[a] The sum of changes from baseline for individual elements do not sum to total change due to rounding and the fact that some impacts when examined jointly can have offsetting effects.

7 DISCUSSION

To our knowledge, this study represents the only bottom-up analysis of therapeutic CMD development costs. As noted in Section 6.1, the only related study we could identify during our literature search and expert consultations was a survey conducted by Stanford University researchers in 2010 on the impact of FDA on medical device innovation in the United States (Makower, et al., 2010). In that study, Makower et al. (2010) surveyed 204 medical device companies and asked the respondents to reflect on their experiences during the clinical development process. Respondents to the survey indicated that "the average total cost from concept to approval" for PMA products was approximately $94 million.

This estimate is not directly comparable to our estimate of $526.4 million (total expected capitalized cost, including post-approval studies). Makower et al. (2010) do not incorporate the cost of failures or the opportunity cost of capital and appears to only include the out-of-pocket cash layout, which we estimate at $54.0 million (i.e., sum of $20 million for non-clinical, $1.4 million for feasibility study, $30.7 million for pivotal study, and $1.9 million for PMA approval stages) exclusive of post-approval studies with our model. The difference in the results of the two studies is attributable to differences in methodology, scope (therapeutic CMDs versus devices developed by targeted small medical device companies), and what is considered as a development cost. For example, Makower et al. (2010) include operational costs incurred during FDA review as part of the PMA approval costs whereas we exclude those in our study. While such costs may be applicable to small device manufacturers with a single product in development, we did not think that this would be the case for medium to large device manufacturers with an established revenue stream from their currently marketed devices. Further insights to the differences in the estimates would require a closer analysis of the survey instrument used and the data collected by those researchers.

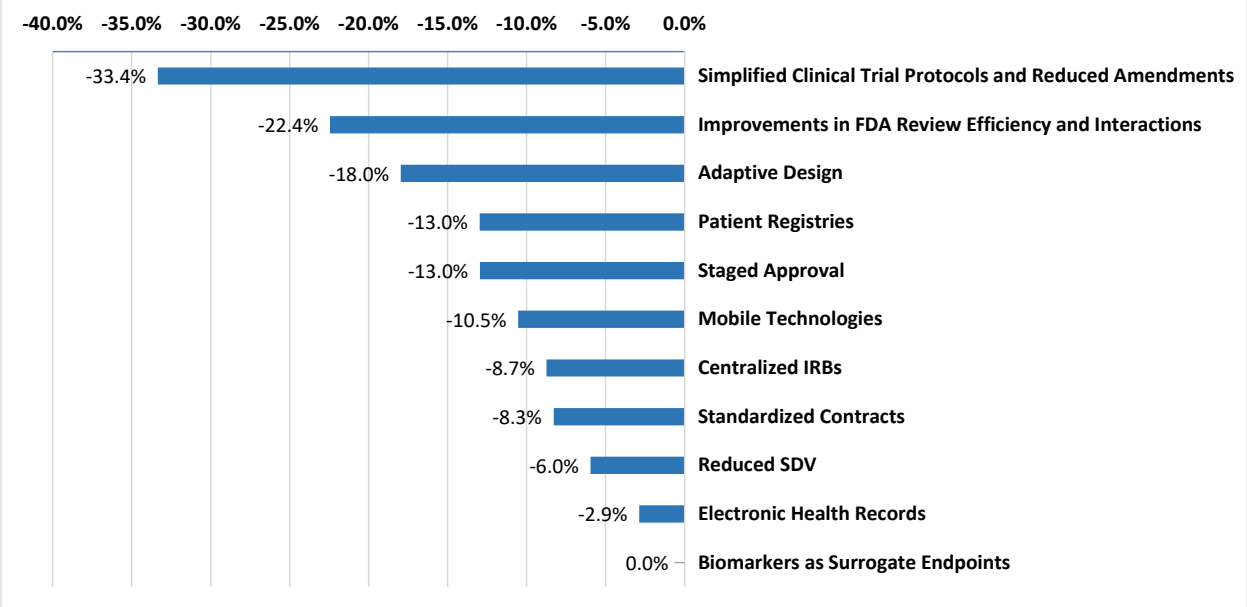
8 CONCLUSIONS

We find that clinical trials comprise the largest portion of overall medical product development costs (Table 8). Clinical phase costs account for around 59 percent of R&D expenditures for therapeutic CMDs. Our estimate of average clinical phase costs, $32.1 million, is approximately half as that of $60.5 million reported in Makower, et al. (2010). When capital costs and the fact that not all products move successfully from one development stage to another are taken into account, the share of non-clinical stage costs rises from 37 percent to 85 percent (Table 8).

Using the information from experts and other relevant data on product development costs, we estimate how implementation of the strategies impact therapeutic CMD development costs (Figure 5). The use of mobile technologies results in time savings in both pivotal and post-approval phases and cost savings for post-approval studies whereas patient registries do not appear to be highly relevant for therapeutic CMD development programs. The strategy with the largest expected impact on overall development costs is simplified clinical trial protocols and reduced amendments (-33.4 percent), followed by improvements in FDA review efficiency

and interactions (-22.4 percent) and use of adaptive design in clinical study designs (-18.0 percent). Those strategies with the lowest expected development cost savings include use of electronic health records (-2.9 percent), reduced SDV (-6.0 percent), and use of standardized contracts (-8.3 percent).

Figure 5. Estimated Impacts on Expected Capitalized Development Costs (Inclusive of Post-approval Costs) for Therapeutic Complex Medical Devices Across Strategies (in Percentages)



Notes: The zero percentages represent those cases where an expert indicated that the strategy was not relevant to a particular phase and/or cost, duration, or probability of phase transition success associated with that phase.

There are several limitations to this study. First, the impact estimates associated with the strategies identified represent the collective opinion of a small expert panel. As with any expert elicitation study, the opinions of experts are subject to known biases, such as availability, over/under-confidence, and representativeness. Second, the mental model each expert used in thinking about a strategy, i.e., what it encompasses and how it is implemented, is unknown but likely highly varied. The cognitive burden of the elicitation, which involved inquiring about hundreds of parameters (Eastern Research Group, Inc., 2022), required a trade-off between depth and breadth, precluding in-depth follow-up discussions with the expert participants. Third, as noted earlier, there have been significant developments in clinical research due to the COVID-19 pandemic that are not captured due to the timing of this study. Significant headway has been made in adopting several strategies highlighted in this study according to recent discussions with experts and federal staff.

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