PREPARED UNDER
ERG TASK ORDER NO. HHSP23337004T
ERG CONTRACT NO. HHSP233201500055I
AND
UNDER SUBCONTRACTS TO
MATHEMATICA POLICY RESEARCH & NORC

DRUG DEVELOPMENT

FINAL

SUBMITTED TO:
U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
OFFICE OF THE ASSISTANT SECRETARY OF PLANNING AND EVALUATION
TRINIDAD BELECHE, PH.D.
200 CONSTITUTION AVE., SW
WASHINGTON, DC 20201

SUBMITTED BY:
EASTERN RESEARCH GROUP, INC.
AYLIN SERTKAYA, PH.D.
CLARA BERGER, B.A.
110 HARTWELL AVENUE
LEXINGTON, MA 02421
WWW.ERG.COM

SEPTEMBER 26, 2024

ACKNOWLEDGMENTS

We gratefully acknowledge Amber Jessup (HHS/OIG/OMP) and Trinidad Beleche (HHS/OS/ASPE) for their leadership, guidance, and input throughout this study. We also would like to thank all of our expert panel members for their input on the potential impacts of different strategies on medical product development costs. Many others involved in clinical research, including pharmaceutical/biopharmaceutical company representatives, CRO personnel, and industry experts, provided valuable information for the study. We are grateful to them all for sharing their opinions and experiences with us. We also would like to acknowledge all federal experts noted below for providing guidance throughout the study and/or reviewing study report and findings.

Hui-Hsing Wong
ASPR/BARDA

Daniel Ramsey
FDA/CDRH/CDRH/OPEQ/OCEA/DCEAI

Chazeman Jackson
(Formerly at ASPE)

Kevin Wood
FDA/OC/OPLIA/OEA/ES

Jessica White
(HHS/ASPE)

Thomas Henry
FDA/OC/OPLIA/OEA/ES

Julie Vaillancourt
FDA/CBER/CBER/OD

Ruben Jacobo-Rubio
FDA/OC/OPLIA/OEA/ES

Owen Faris
FDA/CDRH/CDRH/OPEQ

Kirk Kerr
Formerly at FDA/CDER

Mike Lanthier
FDA/OC/OPLIA/OEA

Jonathan Jarow
Formerly at FDA/CDRH

Murray Sheldon
FDA/CDRH/CDRH/OSPTI

Michael Kurilla
NIH/NCATS/DCI

Peter Stein
FDA/CDER/CDER/OND

Cynthia Boucher
NIH/NCATS/DCI

Ryan Conrad
FDA/CDER/CDER/OSP/OPSA/ES

Petra Kaufmann
(Formerly at NIH/NCATS)

TABLE OF CONTENTS

ACKNOWLEDGMENTS I
TABLE OF CONTENTS II
LIST OF TABLES AND FIGURES III
LIST OF ACRONYMS IV
EXECUTIVE SUMMARY V
1 INTRODUCTION 1
2 STUDY OBJECTIVE 5
3 ANALYTICAL FRAMEWORK 5
4 DATA SOURCES 7
4.1 MEDIDATA SOLUTIONS DATA 7
4.2 IQVIA GRANTPLAN® 7
4.3 CUTTING EDGE (CE) REPORT ON CLINICAL DEVELOPMENT AND TRIAL OPERATIONS 8
4.4 CLINICALTRIALS.GOV DATA 8
4.5 FDA CDER DATA ANALYSIS SEARCH HOST (DASH) DATA 8
5 MODEL PARAMETERS AND ASSUMPTIONS 9
5.1 PHASE DURATIONS 12
5.2 TIME FROM PHASE START TO NEXT PHASE START 12
5.3 AVERAGE NUMBER OF PATIENTS ENROLLED PER TRIAL 16
5.4 AVERAGE NUMBER OF TRIALS CONDUCTED IN SUPPORT OF AN FDA NDA/BLA APPLICATION 18
5.5 AVERAGE COST PER PATIENT 19
5.6 PHASE TRANSITION SUCCESS PROBABILITIES 21
5.7 OPPORTUNITY COST OF CAPITAL 26
5.8 OUT-OF-POCKET COST ESTIMATES 27
5.9 RESULTS 28
5.10 BASELINE DEVELOPMENT COST ESTIMATES 28
5.11 IMPACT OF SELECT CLINICAL TRIAL STRATEGIES ON THE TOTAL COST OF DRUG DEVELOPMENT 35
6 DISCUSSION 43
7 CONCLUSIONS 43
8 REFERENCES 45
APPENDIX A – DETAILED EXPERT ESTIMATES OF STRATEGY IMPACTS ON COST, DURATION, AND PROBABILITY OF PHASE TRANSITION SUCCESS FOR DRUGS, BY THERAPEUTIC AREA A-1

LIST OF TABLES AND FIGURES

Table 1. Model Therapeutic Areas Mapped onto Clinicaltrials.gov Therapeutic Categories 9
Table 2. Summary of Drug Development Cost Model Parameters and Assumptions, by Therapeutic Area and Phase 10
Table 3. Average Phase Durations (in Months), by Therapeutic Area 13
Table 4. Average Number of Patients per Trial, by Therapeutic Area 17
Table 5. Average Number of Trials Conducted in Support of an FDA NDA/BLA Application, by Therapeutic Area and Phase 19
Table 6. Average Per-patient Costs (in 2018 $), by Therapeutic Area and Phase 20
Table 7. Transition Success Probabilities, by Therapeutic Area and Phase 23
Table 8. Published Estimates of Opportunity Cost of Capital 26
Table 9. Sensitivity Analysis of Varying Assumptions on Non-clinical to Clinical R&D Ratio, R, on Overall Cost Estimates 28
Table 10. Recent Published Estimates of Cost of Drug Development 30
Table 11. Average Cost of Developing a Drug for the U.S. Market (in Million $ 2018) 31
Table 12. Expert Estimates of Strategy Impacts on Cost, Duration, and Probability of Phase Transition Success for Drugs (All Therapeutic Areas Combined) 36
Table 13. Impacts of Clinical Trial Strategies on Baseline Cost, Duration, and Phase Transition Success Probability – Drugs 38
Figure 1. Overview of Drug Development 2
Figure 3. Estimated Impacts on Expected Capitalized Development Costs (Inclusive of Post-approval Costs) for Drugs Across Strategies (in Percentages) 45

LIST OF ACRONYMS

ASPE	Office of The Assistant Secretary for Planning and Evaluation
BLA	Biologics license application
CROs	Contract research organization
CTTI	Clinical Trials Transformation Initiative
EHR	Electronic health record
EMR	Electronic medical record
ERG	Eastern Research Group, Inc.
FDA	Food and Drug Administration
HHS	Department of Health and Human Services
IND	Investigational new drug
IRB	Institutional review board
NDA	New drug application
NIH	National Institutes of Health
NME	New molecular entity
OCOC	Opportunity cost of capital
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. In drug development, the clinical phase lasts an average of around 95 months compared to 31 months for the non-clinical phase and accounts for 69 percent of overall R&D costs (DiMasi, et al., 2016). 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 drug 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 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.

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 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 drug applications (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 drugs. Our model used data from a variety of sources (public and non-public) and widely accepted accounting methods. We estimate the average

out-of-pocket cost per drug at $172.7 million, which is significantly lower than published findings that used data reported by primarily large pharmaceutical companies. After accounting for cost of failures and capital, our estimate of $879.3 million is also generally lower than most published estimates. Our analysis also shows that clinical trials comprise the largest portion of overall drug development costs at $117.4 million which accounts for around 68 percent of out-of-pocket R&D expenditures.[1]

The strategy with the largest expected impact on overall development costs across all therapeutic areas is Improvements in FDA Review Process Efficiency and Interactions (-27.1 percent), followed by Adaptive Design (-22.8 percent), and implementation of a Simplified Clinical Trial Protocols and Reduced Amendments (-22.2 percent). Those strategies with the lowest expected development cost savings across all therapeutic areas include Use of Patient Registries (-9.9 percent), use of Biomarkers as Surrogate Endpoints (-13.3 percent), Electronic Health Records (-13.6 percent), and use of Standardized Contracts (-14.8 percent).

[1] The model details and key findings regarding development costs are also available at Sertkaya, et al. (2016).

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. Clinical trials constitute a major portion of the overall duration and cost of medical product development.[2] According to one study, the clinical phase of drug development lasts an average of around 95 months compared to 31 months for the non-clinical phase and accounts for 69 percent of R&D costs (DiMasi, et al., 2016). The same (2016) study estimates the average cost of clinical trials for an FDA-approved new drug at $339.3 million in 2013 dollars overall with Phase 1 accounting for 7.5 percent ($25.3 million), Phase 2 for 17.3 percent ($58.6 million), and Phase 3 for 75.3 percent ($255.4 million). Although there is disagreement on the magnitude of these clinical trial costs,[3] most agree that they comprise a large portion of overall development costs for drugs.

Figure 1 depicts a stylized model of the drug development process from conception through post marketing activities. The initial phase of development begins with the exploratory stage which includes identification and validation of a "druggable" target for a specific disease (A—Target Discovery in Figure 1).[4] Once a target candidate is identified and validated, the developer uses screening approaches to identify a "hit" compound (i.e., a compound that interacts with the target of interest) using such strategies as high-throughput screening, phenotypic screening, virtual screening, fragment-based screening and structure-based design (B—Hit Generation) (Lansdowne, 2020). Next, the developer works on refining these "hits" to optimize their pharmacokinetic properties while also investigating their "off-target" interactions to get a sense of potential adverse effects (C—Lead Identification). After optimizing the lead compound (D—Lead Optimization), preclinical in-vitro and in-vivo testing (E—Animal Testing) is conducted to begin accumulating evidence of the compound's biological affect (U.S. Food and Drug Administration, 2018b). The developer then uses animal models to answer such questions as "What does the drug do to the body?, What does the body do to the drug?, and It is potent, but is it safe?" (Lansdowne, 2020).

Upon completion of early discovery and preclinical testing (Stages A through E in Figure 1), the developer must submit an investigational new drug (IND) application to the FDA before clinical testing on human subjects may begin (F—FDA IND Submission). The IND application includes "…animal study data and toxicity (side effects that cause great harm) data;

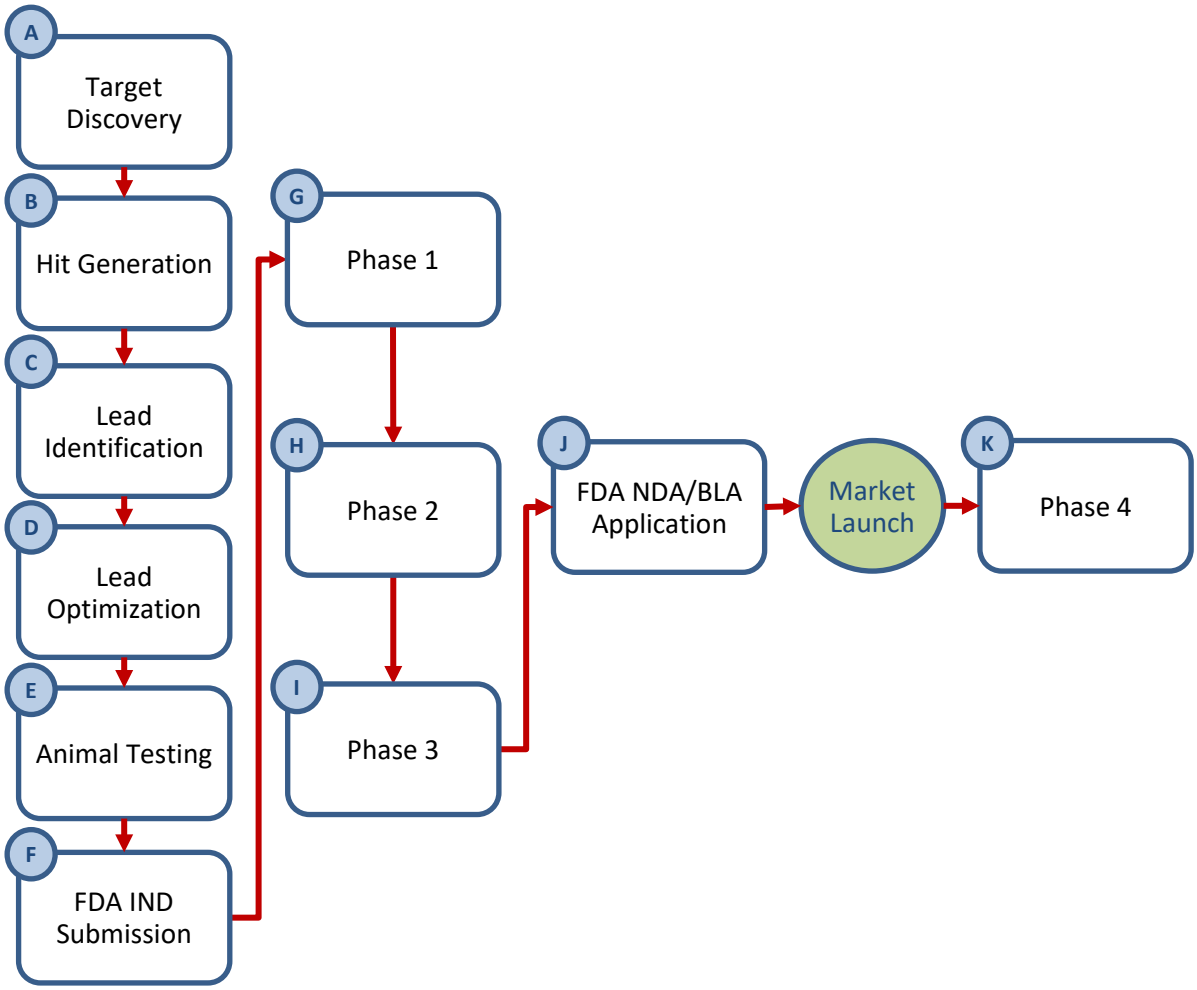
[2] We acknowledge that strategies for the identification of new compounds (e.g., high-throughput screening, in silico testing, etc.) in early drug discovery could also have sizable impacts on total development costs. However, such strategies were deemed out of scope for this study given our focus on the clinical research phase.

[3] A 2018 study by Moore, et al. found that the median pivotal trial costs for new drugs approved by FDA during the 2015-2016 period was much lower than the frequently-cited estimates. After examining 138 pivotal trials that covered 59 different drugs, the authors estimated the median cost of a pivotal trial at $19 million (interquartile range, $12.2 million-$33.1 million) as opposed to the $255.4 million estimate reported in DiMasi, et al. (2016). A more recent follow-up study conducted by the same group estimated the median cost of pivotal trials for oncology drugs at $31.7 million (interquartile range = $17.0-$60.4 million) (Hsiue, et al., 2020). The term pivotal trial is often associated with a Phase 3 study but can also refer to a Phase 2 study under limited circumstances.

[4] A target is deemed "druggable" if its activity can be altered by a therapeutic agent (Lansdowne, 2020).

manufacturing information; clinical protocols (study plans) for studies to be conducted; data from any prior human research; and information about the investigator." (U.S. Food and Drug Administration, 2018b). FDA reviews the IND and must inform the sponsor of any issues that would delay or suspend the proposed clinical investigation at or before 30 days from receipt of the IND. The sponsor may begin testing on humans under the specified IND number, once FDA determines that there are no outstanding issues in the information provided in the original IND that would delay or suspend the proposed clinical study.

Figure 1. Overview of Drug Development



Once clinical investigation under the sponsor's IND is allowed to proceed, the sponsor may then begin the next phase in development, the clinical stage (Stages G through I in Figure 1), which usually consists of three clinical phases. Phase 1 clinical studies test for safety and dosing among a small group (20 to 100) of closely monitored subjects who are either healthy or have the disease or condition. Phase 2 studies enroll several hundred subjects that have the disease or condition and provide additional information on safety and dosing as well as early evidence of efficacy and adverse events. Phase 3 studies enroll 300 to 3,000 or more subjects with the disease or condition and provide a thorough assessment of safety and efficacy of the

drug (U.S. Food and Drug Administration, 2018b). To support approval, drug safety and efficacy are usually demonstrated through well-controlled randomized and double-blind trials. Occasionally, the sponsor must conduct a large-scale noninferiority study for a new drug that is the same general type as a drug already on the market (U.S. Food and Drug Administration, 2016a).

Upon completion of clinical trials to support approval, the developer then submits a New Drug Application (NDA) to FDA's Center for Drug Evaluation and Research (CDER) if the drug is a pharmaceutical or a Biologics License Application (BLA) to CDER or FDA's Center for Biologics Evaluation and Research (CBER) if the drug is a biologic.[5] The application must demonstrate safety and efficacy, as well as an acceptable manufacturing process, which is confirmed through a manufacturing facility inspection. Once the appropriate center conducts a scientific review, the applicable FDA product advisory committee may be asked to reviews and comment on the benefit-to-risk ratio of the drug for FDA's consideration in taking an action (U.S. Food and Drug Administration, 2020b). An approved marketing application allows the developer to bring the drug to the market for one or more labeled indication(s). Once on the market, the drug enters the post-marketing stage, which may include conducting Phase 4 studies to investigate rare cases and to monitor adverse events; studying the safety and efficacy of the drug on pediatric populations; and submitting batch manufacturing samples to FDA for potency, safety, and purity tests.

Given the relatively large contribution of clinical phase to overall development costs, strategies with potential to reduce time and cost of conducting drug clinical trials are important. In a previous study, we identified several promising strategies with potential to improve drug 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.

[5] In 2003, FDA transferred some of the therapeutic biological products under CBER's purview to CDER, These products include "…monoclonal antibodies for in vivo use; proteins intended for therapeutic use, including cytokines (e.g. interferons), enzymes (e.g. thrombolytics), and other novel proteins, except for those that are specifically assigned to CBER (e.g., vaccines and blood products); Immunomodulators (non-vaccine and non-allergenic products intended to treat disease by inhibiting or modifying a pre-existing immune response); [and] growth factors, cytokines, and monoclonal antibodies intended to mobilize, stimulate, decrease or otherwise alter the production of hematopoietic cells in vivo" (U.S. Food and Drug Administration, 2018j).

- **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 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.

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 noted in Section 1 above on development costs, we first need estimates of baseline development costs for drugs. 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.

Drug 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. For the purpose of this analysis, we broke down the overall development of a drug as shown in Figure 1, into six distinct phases, including 1—non-clinical, which includes all steps in between target discovery (Stage A) and FDA IND approval (Stage F), 2—Phase 1, 3—Phase 2, 4—Phase 3, 5—FDA review, and 6—Phase 4. 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.,

$$E(C_i) = \frac{C_i}{p_i} \tag{1}$$

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 drug is given by:

$$CC_i = \int_{t_{i,e}}^{t_{i,b}} \left(\frac{C_i}{t_i}\right)(e^{rt})\mathrm{d}t \tag{2}$$

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:

$$CC_i = \left[\frac{(C_i/t_i)}{r}\right](e^{rt_{i,b}} - e^{rt_{i,e}}) \quad (3)$$

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:

$$E(CC_i) = \frac{CC_i}{p_i} \quad (4)$$

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

$$E(CC) = \sum_{i=1}^{n} E(CC_i) \quad (5)$$

where i = non-clinical, Phase 1, Phase 2, Phase 3, FDA review, and Phase 4.

For example, suppose the total out of pocket cash outlay for Phase 2 is $5.0 million for a given drug x and the probability of the drug making it to market given that it is in Phase 2 is 40 percent, then the expected cost of Phase 2, $E(C_2)$, that accounts for failures is $12.5 million, i.e.,

$$E(C_2) = \frac{C_2}{p_2} = \frac{\$5.0}{0.40} = \$12.5 \text{ million} \quad (6)$$

If we further assume that the cost of capital, r, is 1 percent per month (i.e., 12 percent per annum) and that Phase 2 lasts 35 months ($t_2 = 35$) begins 105 months before drug launch ($t_2^b = 105$) and ends 71 months before drug launch ($t_2^e = 71$) then the capitalized cost of Phase 2, CC_2, that accounts for the opportunity cost of the investment in drug x is $11.8 million, i.e.,

$$CC_2 = \left[\frac{(C_2/t_2)}{r}\right](e^{rt_{2,b}} - e^{rt_{2,e}}) = \left[\frac{\$5.0/35}{0.01}\right](e^{0.01\times 105} - e^{0.01\times 71}) = \$11.8 \text{ million} \quad (7)$$

Using the above equations, we can compute the expected capitalized cost of Phase 2, $E(CC_2)$, as $29.4 million:

$$E(CC_2) = \frac{CC_2}{p_2} = \frac{\$11.8}{0.40} = \$29.4 \text{ million} \quad (8)$$

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

4 DATA SOURCES

We describe the primary data sources used in the modeling in the following sections. In addition to these data sources, we also used published studies to support our parameter estimates and assumptions. These are noted in those sections where applicable.

4.1 MEDIDATA SOLUTIONS DATA

We used a custom tabulation from three proprietary databases on clinical trial costs, which are offered by Medidata Solutions:[6]

- 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 with clinical trials, including cost of IRB approvals, cost of protocols, patient recruitment costs, and administrative staff costs among others by therapeutic area.[7]

4.2 IQVIA GRANTPLAN®

IQVIA's GrantPlan is a large database of current clinical investigator budgets from 62 countries. The database contains cost data compiled from final negotiated budgets between sponsors and investigator sites at the procedure, cost per visit, and cost per patient levels from countries involved in drug testing throughout North America, Europe, Asia, and Latin America.

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

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

The database includes cost information from 48 sponsors and 12 CROs that conduct 76 percent of all global clinical trials. We obtained a custom tabulation from this proprietary database that provided cost per patient estimates by therapeutic area, phase, and country along with applicable overhead benchmarks covering the period from 2015 through 2019.

4.3 CUTTING EDGE (CE) REPORT ON CLINICAL DEVELOPMENT AND TRIAL OPERATIONS

Cutting Edge (CE), LLC periodically publishes a study on clinical development and trial operations protocol design and cost per patient benchmarks. CE collects the data for their study via a survey supplemented with interviews. CE's 2013 report contained information gathered from over 140 clinical trials conducted by pharmaceutical and biotechnology companies as well as CROs of varying sizes and geographic locations (Cutting Edge Information, LLC, 2013). We used the cost per patient estimates reported in their 2013 publication across different therapeutic areas.

4.4 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 our model. We used a snapshot of the clinicaltrials.gov data downloaded on June 24, 2020 (i.e., the monthly archived data file titled, "20200624_pip-delimited-export.zip") through the Clinical Trials Transformation Initiative's (CTTI) Access to Aggregate Content of ClinicalTrials.gov (AACT) initiative. The database included 343,555 unique NCT IDs.

Next, we subset the downloaded data to contain only those studies that 1) were completed between January 1, 2014 through June 24, 2020; 2) were interventional in nature ; 3) where the intervention was a drug; and 4) had a category that corresponded to one or more of the 13 therapeutic areas in our model (Table 1). The selection criteria resulted in a total of 10,307 unique research studies. Of these studies, we excluded 13 percent (1,303 studies) because they were either an early phase 1 study (195 out of 1.303 studies) or did not specify the study phase (1,108 out of 1,303 studies). Of the remaining 9,004 studies, 25 percent were Phase 1, 30 percent were Phase 2, 23 percent were Phase 3, and 22 percent were Phase 4.

4.5 FDA CDER DATA ANALYSIS SEARCH HOST (DASH) DATA

Data Analysis Search Host (DASH) is a database built by FDA CDER for monitoring and querying the progress of applications submitted for CDER review. DASH consolidates key data—including details about the medical products themselves as well as every stage of development through FDA's regulatory process—for INDs, NDAs, and BLAs from 2007 to present. While the database contains nearly 100 fields associated with each new molecular entity (NME) NDA and original BLA, not all data can be shared publicly. Thus, we worked with CDER to build a custom tabulation of select fields and appropriate level of aggregation for use in our model. Our custom query covered data 2007 through August 2017 and included

approved products only. For products with multiple review cycles, only data from the most recent review cycle was provided.

Table 1. Model Therapeutic Areas Mapped onto Clinicaltrials.gov Therapeutic Categories

Model Therapeutic Area	Clinicaltrials.gov Therapeutic Category
Anti-Infective	Bacterial and Fungal Diseases
	Parasitic Diseases
	Viral Diseases
Cardiovascular	Heart and Blood Diseases
Central Nervous System	Behaviors and Mental Disorders
	Nervous System Diseases
	Substance Related Disorders
Dermatology	Skin and Connective Tissue Diseases
Endocrine	Gland and Hormone Related Diseases
	Nutritional and Metabolic Diseases
Gastrointestinal	Digestive System Diseases
Genitourinary System	Urinary Tract, Sexual Organs, and Pregnancy Conditions
Hematology	Blood and Lymph Conditions
Immunomodulation	Immune System Diseases
	Muscle, Bone, and Cartilage Diseases
Oncology	Cancers and Other Neoplasms
Ophthalmology	Eye Diseases
Pain and Anesthesia	[a]
Respiratory System	Respiratory Tract (Lung and Bronchial) Diseases
Not Mapped	Diseases and Abnormalities at or Before Birth
	Disorders of Environmental Origin
	Ear, Nose, and Throat Diseases
	Mouth and Tooth Diseases
	Occupational Diseases
	Symptoms and General Pathology
	Wounds and Injuries

[a] None of the broad therapeutic areas listed in the "category" field of clinicaltrials.gov directly corresponded to "pain and anesthesia." To include those studies, we searched for those studies that mentioned "pain" and/or "anesthesia" in the "condition" field and mapped them onto our model's pain and anesthesia therapeutic area.

5 MODEL PARAMETERS AND ASSUMPTIONS

Table 2 presents the parameter estimates and assumptions for our drug development cost model. We discuss the basis for these estimates in the following sections. Because our model encompasses 13 different therapeutic areas, we generally address the overall average across all therapeutic areas, presented in the right-most column, in the below discussions for brevity.

Table 2. Summary of Drug Development Cost Model Parameters and Assumptions, by Therapeutic Area and Phase

Parameter	Phase	Anti-Infective	Cardiovascular	Central Nervous System	Dermatology	Endocrine	Gastrointestinal	Genitourinary System	Hematology	Oncology	Respiratory System	Ophthalmology	Pain and Anesthesia	Immunomodulation	All Therapeutic Areas
Start to Start (in Months)	Non-clinical to Phase 1	31.2	31.2	31.2	31.2	31.2	31.2	31.2	31.2	31.2	31.2	31.2	31.2	31.2	**31.2**
	Phase 1 to Phase 2	12.9	8.5	11.7	16.6	7.7	16.6	7.4	14.2	19.1	10.5	10.7	16.6	7.9	**16.6**
	Phase 2 to Phase 3	22.4	30.4	32.1	27.2	23.4	27.2	20.6	28.0	32.2	29.7	21.6	27.2	26.5	**27.2**
	Phase 3 to FDA review	22.3	28.6	30.8	25.9	24.2	25.9	22.4	39.7	39.3	28.7	22.9	25.9	24.7	**25.9**
	FDA BLA/NDA review to approval	14.8	19.1	21.0	12.2	18.8	17.9	18.3	15.3	9.6	18.9	11.9	31.7	16.8	**16.2**
Phase Durations (in months)	Non-clinical	31.2	31.2	31.2	31.2	31.2	31.2	31.2	31.2	31.2	31.2	31.2	31.2	31.2	**31.2**
	Phase 1	21.5	14.1	19.5	27.8	12.9	27.8	12.4	23.8	31.9	17.6	17.9	27.8	13.1	**27.8**
	Phase 2	28.0	38.0	40.1	34.0	29.3	34.0	25.8	35.0	40.3	37.1	27.0	34.0	33.1	**34.0**
	Phase 3	32.8	42.0	45.3	38.0	35.6	38.0	33.0	58.3	57.7	42.2	33.7	38.0	36.3	**38.0**
	FDA BLA/NDA review	14.8	19.1	21.0	12.2	18.8	17.9	18.3	15.3	9.6	18.9	11.9	31.7	16.8	**16.2**
	Phase 4	38.7	38.5	35.0	36.6	34.0	36.6	29.9	36.6	45.7	36.6	30.7	36.6	39.6	**36.6**
Per-patient Cost (in $ 2018)	Non-clinical	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	**NA**
	Phase 1	$19,399	$59,456	$87,390	$35,450	$85,463	$61,848	$53,770	$349,363	$103,344	$44,330	$50,999	$90,370	$63,471	**$81,338**
	Phase 2	$59,289	$41,323	$48,767	$66,661	$51,556	$63,590	$45,781	$100,554	$78,753	$43,563	$48,438	$77,726	$47,897	**$58,618**
	Phase 3	$30,001	$33,084	$39,612	$48,587	$48,753	$47,656	$38,930	$118,473	$93,145	$46,764	$79,933	$60,751	$54,909	**$53,180**
	FDA BLA/NDA review	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	**NA**
	Phase 4	$13,814	$33,915	$34,956	$33,102	$56,824	$52,746	$16,699	$41,958	$23,515	$18,987	$24,022	$41,573	$30,246	**$35,190**
Number of Patients Enrolled per Trial	Non-clinical	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	**NA**
	Phase 1	69	42	44	106	38	38	50	31	58	49	121	36	55	**51**
	Phase 2	243	189	243	133	225	292	323	134	137	203	299	270	323	**235**
	Phase 3	575	1,151	529	568	414	496	546	233	293	516	876	1,209	309	**630**
	FDA BLA/NDA review	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	**NA**
	Phase 4	1,430	508	356	850	482	1,344	410	411	261	1,159	413	280	383	**708**
Average Number of Trials	Non-clinical	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	**NA**
	Phase 1	2	2	2	2	2	2	2	2	1	1	1	2	2	**2**
	Phase 2	2	1	1	2	2	1	1	2	1	2	2	2	2	**2**
	Phase 3	2	2	3	3	4	2	1	2	2	4	2	3	3	**3**
	FDA BLA/NDA review	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	**NA**
	Phase 4	2	2	2	1	2	2	1	2	1	2	2	1	2	**2**

Parameter	Phase	Anti-Infective	Cardiovascular	Central Nervous System	Dermatology	Endocrine	Gastrointestinal	Genitourinary System	Hematology	Oncology	Respiratory System	Ophthalmology	Pain and Anesthesia	Immunomodulation	All Therapeutic Areas
Transition Success Probabilities (%)	Non-clinical to Phase 1	68.0%	68.0%	68.0%	68.0%	68.0%	68.0%	68.0%	68.0%	68.0%	68.0%	68.0%	68.0%	68.0%	**68.0%**
	Phase 1 to Phase 2	65.9%	65.0%	61.5%	60.2%	68.0%	71.6%	62.9%	73.3%	61.5%	68.5%	86.0%	60.2%	69.9%	**60.2%**
	Phase 2 to Phase 3	49.6%	37.1%	33.1%	35.9%	46.3%	35.3%	44.9%	56.6%	26.8%	27.4%	52.7%	35.9%	40.1%	**35.9%**
	Phase 3 to FDA review	74.1%	57.6%	55.9%	65.5%	63.9%	55.3%	71.4%	75.0%	42.7%	75.6%	58.3%	65.5%	65.4%	**65.5%**
	FDA BLA/NDA review to approval	94.4%	75.5%	87.0%	88.3%	81.3%	86.2%	85.7%	84.0%	85.5%	89.5%	77.5%	88.3%	95.3%	**88.3%**
Out of Pocket Cost Estimates (in $ 2018 million)	Non-clinical	$9.4	$10.1	$8.7	$9.3	$14.2	$11.4	$7.7	$17.9	$7.0	$9.0	$32.0	$22.2	$11.6	**$11.8**
	Phase 1	$2.8	$4.2	$6.8	$6.5	$6.8	$4.3	$4.2	$17.3	$8.1	$3.2	$7.6	$6.1	$6.8	**$7.1**
	Phase 2	$22.3	$11.2	$16.1	$14.9	$19.4	$26.2	$19.8	$22.1	$14.5	$13.7	$22.8	$34.6	$24.3	**$21.0**
	Phase 3	$41.6	$91.2	$59.4	$70.6	$85.8	$58.1	$31.3	$61.9	$37.7	$90.5	$173.0	$214.4	$52.4	**$89.3**
	FDA BLA/NDA review to approval	$2.6	$2.6	$2.6	$2.6	$2.6	$2.6	$2.6	$2.6	$2.6	$2.6	$2.6	$2.6	$2.6	**$2.6**
Cost of Capital (%)		11.0%													

NA = Not applicable

Note that all values are rounded up to the nearest whole number.

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 represents the time it takes from synthesis of the compound to the start of human trials, which includes early exploratory research for target discovery, hit generation and target identification; lead optimization; preclinical work involving animal testing to develop dosing and toxicity models; and obtaining an IND approval from FDA to begin testing in human subjects. We used published studies and information compiled from FDA's DASH database to estimate average phase durations across all development stages (Table 3) by therapeutic area. From Table 3, Phase 3 is the longest (38.0 months) drug development stage across all therapeutic areas followed by post-approval Phase 4 (36.6 months), Phase 2 (34.0 months), non-clinical stage (31.2 months), and Phase 1 (27.8 months). The average time for the FDA review phase is 16.2 months. This includes the time the sponsor spends on responding to any questions and/or information requests from the FDA as well as preparing major/minor amendments, if needed. Thus, the estimate does not solely reflect the time FDA spends on reviewing the application. While there is variation in phase durations across the different therapeutic areas, this ranking is generally stable with Phase 3 comprising the longest stage and FDA review the shortest one.

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., Phase 2) and the start of the next development phase (e.g., Phase 3) supporting an application. For the non-clinical phase to Phase 1 estimate, we assumed that Phase 1 will begin immediately upon successful completion of the non-clinical development phase and receipt of IND approval from FDA. Similarly, for the FDA review to approval estimate, we used the estimates reported in Table 3 by therapeutic area (ranging from 9.6 months for oncology to 31.7 months for pain and anesthesia drugs). For the clinical phases, work on the clinical phases may overlap. In other words, the sponsor may begin Phase 2 clinical trials before completing the Phase 1 clinical trials. DiMasi et al. (2016) estimated the average phase duration, t_i, and average time to next phase, t_{i-j}, where i = 1, 2, 3, and j = 2, 3, FDA BLA/NDA review, for each of the three clinical phases as:

- t_1 = 33.1 months; t_{1-2} = 19.8 months
- t_2 = 37.9 months; t_{2-3} = 30.3 months
- t_3 = 45.1 months; $t_{3-FDA\ BLA/NDA\ Review}$ = 30.7 months

To estimate the average phase start to next phase start durations, we used the DiMasi et al. (2016) estimates along with our phase duration estimates. For example, the average Phase 1 length for the Anti-Infective therapeutic area is 21.5 months (Table 3). Then, we estimated the average time to Phase 2 as the product of estimated average Phase 1 length (21.5 months) and the ratio of average time to Phase 2 to average Phase 1 length (19.8 ÷ 33.1 months) as reported in DiMasi et al. (2016) at 12.9 months (= 21.5 × [19.8 ÷ 33.1] months).

Table 3. Average Phase Durations (in Months), by Therapeutic Area

Source	Time Period	Therapeutic Area	Therapeutic Area in the Original Source [a]	Non-clinical	Phase 1	Phase 2	Phase 3	FDA BLA/NDA Review	Phase 4
Wong et al (2019)	2000-2015	Anti-Infective	Infectious Disease	NA	18.4	31.2	35.0	NA	38.7
BiomedTracker (2016)	2006-2015		Infectious Disease	NA	NA	NA	NA	16.8	NA
FDA DASH Query (2018l)	2007-2017		Anti-Infective	NA	NA	NA	NA	12.9	NA
Abrantes-Metz et al (2004)	1989-2002		Anti-HIV/AIDS	NA	24.7	24.8	30.6	NA	NA
Wong et al (2019)	2000-2015	Cardiovascular	Cardiovascular	NA	12.4	33.6	39.6	NA	38.5
BiomedTracker (2016)	2006-2015		Cardiovascular	NA	NA	NA	NA	16.8	NA
FDA DASH Query (2018l)	2007-2017		Cardiovascular	NA	NA	NA	NA	21.5	NA
Abrantes-Metz et al (2004)	1989-2002		Anti-Hypertension	NA	15.9	42.5	44.4	NA	NA
Wong et al (2019)	2000-2015	Central Nervous System	Central Nervous System	NA	11.0	30.6	33.9	NA	35.0
BiomedTracker (2016)	2006-2015		Neurology	NA	NA	NA	NA	23.9	NA
BiomedTracker (2016)	2006-2015		Psychiatry	NA	NA	NA	NA	19.1	NA
FDA DASH Query (2018l)	2007-2017		Central Nervous System	NA	NA	NA	NA	19.8	NA
Abrantes-Metz et al (2004)	1989-2002		Anti-Alzheimer's Disease	NA	23.2	46.9	41.8	NA	NA
Abrantes-Metz et al (2004)	1989-2002		Anti-Parkinson's Disease	NA	24.4	42.9	60.1	NA	NA
FDA DASH Query (2018l)	2007-2017	Dermatology	Dermatology	NA	NA	NA	NA	12.2	NA
Wong et al (2019)	2000-2015	Endocrine	Metabolic Diseases	NA	10.7	31.0	32.0	NA	34.0
Wong et al (2019)	2000-2015		Endocrinology	NA	10.7	31.0	32.0	NA	34.0
BiomedTracker (2016)	2006-2015		Metabolic Diseases	NA	NA	NA	NA	18.0	NA
BiomedTracker (2016)	2006-2015		Endocrinology	NA	NA	NA	NA	21.5	NA
FDA DASH Query (2018l)	2007-2017		Endocrine	NA	NA	NA	NA	16.9	NA
Abrantes-Metz et al (2004)	1989-2002		Anti-Diabetes	NA	17.4	25.8	42.7	NA	NA
BiomedTracker (2016)	2006-2015	Gastrointestinal	Gastroenterology	NA	NA	NA	NA	21.5	NA
FDA DASH Query (2018l)	2007-2017		Gastrointestinal	NA	NA	NA	NA	14.2	NA
Wong et al (2019)	2000-2015	Genitourinary System	Genitourinary	NA	12.4	25.8	33.0	NA	29.9
BiomedTracker (2016)	2006-2015		Urology	NA	NA	NA	NA	20.4	NA
FDA DASH Query (2018l)	2007-2017		Genitourinary System	NA	NA	NA	NA	16.2	NA
BiomedTracker (2016)	2006-2015	Hematology	Hematology	NA	NA	NA	NA	19.1	NA
FDA DASH Query (2018l)	2007-2017		Hematology	NA	NA	NA	NA	11.5	NA
Abrantes-Metz et al (2004)	1989-2002		Anti-Thrombosis	NA	23.8	35.0	58.3	NA	NA
Wong et al (2019)	2000-2015	Immunomodulation	Autoimmune Diseases	NA	11.0	32.1	32.1	NA	39.6
Wong et al (2019)	2000-2015		Inflammation	NA	11.0	32.1	32.1	NA	39.6
BiomedTracker (2016)	2006-2015		Autoimmune Diseases	NA	NA	NA	NA	19.1	NA
FDA DASH Query (2018l)	2007-2017		Immunomodulation	NA	NA	NA	NA	14.5	NA

Source	Time Period	Therapeutic Area	Therapeutic Area in the Original Source [a]	Non-clinical	Phase 1	Phase 2	Phase 3	FDA BLA/NDA Review	Phase 4
Abrantes-Metz et al (2004)	1989-2002		Anti-Arthritis	NA	17.5	35.1	44.8	NA	NA
Wong et al (2019)	2000-2015	Oncology	Oncology	NA	39.9	48.9	68.2	NA	45.7
BiomedTracker (2016)	2006-2015		Oncology	NA	NA	NA	NA	13.2	NA
FDA DASH Query (2018l)	2007-2017		Oncology	NA	NA	NA	NA	5.9	NA
Abrantes-Metz et al (2004)	1989-2002		Anti-Cancer	NA	23.8	31.7	47.1	NA	NA
Wong et al (2019)	2000-2015	Ophthalmology	Ophthalmology	NA	17.9	27.0	33.7	NA	30.7
BiomedTracker (2016)	2006-2015		Ophthalmology	NA	NA	NA	NA	15.6	NA
FDA DASH Query (2018l)	2007-2017		Ophthalmology	NA	NA	NA	NA	8.3	NA
FDA DASH Query (2018l)	2007-2017	Pain and Anesthesia	Pain and Anesthesia	NA	NA	NA	NA	31.7	NA
BiomedTracker (2016)	2006-2015	Respiratory System	Allergy	NA	NA	NA	NA	15.6	NA
BiomedTracker (2016)	2006-2015		Respiratory	NA	NA	NA	NA	19.1	NA
FDA DASH Query (2018l)	2007-2017		Respiratory System	NA	NA	NA	NA	21.9	NA
Abrantes-Metz et al (2004)	1989-2002		Anti-Asthma	NA	17.6	37.1	42.2	NA	NA
Wong et al (2019)	2000-2015	All Therapeutic Areas	Overall	NA	19.3	35.2	46.0	NA	NA
BiomedTracker (2016)	2006-2015		Overall	NA	NA	NA	NA	19.1	NA
FDA DASH Query (2018l)	2007-2017		Overall	NA	NA	NA	NA	13.6	NA
Martin, Hutchens, & Hawkins (2017)	2006-2008		Overall	NA	30.9	32.9	32.9	NA	NA
Martin, Hutchens, & Hawkins (2017)	2007-2009		Overall	NA	32.9	32.9	34.9	NA	NA
Martin, Hutchens, & Hawkins (2017)	2008-2010		Overall	NA	30.9	33.9	34.9	NA	NA
Martin, Hutchens, & Hawkins (2017)	2009-2011		Overall	NA	30.9	33.9	33.9	NA	NA
Martin, Hutchens, & Hawkins (2017)	2010-2012		Overall	NA	27.0	34.9	36.9	NA	NA
Martin, Hutchens, & Hawkins (2017)	2011-2013		Overall	NA	29.0	32.9	41.9	NA	NA
Martin, Hutchens, & Hawkins (2017)	2012-2014		Overall	NA	30.9	35.9	40.9	NA	NA
Martin, Hutchens, & Hawkins (2017)	2013-2015		Overall	NA	31.9	39.9	38.9	NA	NA
DiMasi, Grabowski, Hansen, (2016)	NA		Overall	31.2	19.8	30.3	30.7	16.0	NA
Abrantes-Metz et al (2004)	1989-2002		Overall	NA	22.0	31.6	45.9	NA	NA
Anti-Infective Average				**31.2 [b]**	**21.5**	**28.0**	**32.8**	**14.8**	**38.7**
Cardiovascular Average					**14.1**	**38.0**	**42.0**	**19.1**	**38.5**
Central Nervous System Average					**19.5**	**40.1**	**45.3**	**21.0**	**35.0**
Dermatology Average					**27.8 [b]**	**34.0 [b]**	**38.0 [b]**	**12.2**	**36.6 [b]**
Endocrine Average					**12.9**	**29.3**	**35.6**	**18.8**	**34.0**
Gastrointestinal Average					**27.8 [b]**	**34.0 [b]**	**38.0 [b]**	**17.9**	**36.6 [b]**
Genitourinary System Average					**12.4**	**25.8**	**33.0**	**18.3**	**29.9**
Hematology Average					**23.8**	**35.0**	**58.3**	**15.3**	**36.6 [b]**

Source	Time Period	Therapeutic Area	Therapeutic Area in the Original Source [a]	Non-clinical	Phase 1	Phase 2	Phase 3	FDA BLA/NDA Review	Phase 4
Oncology Average					**31.9**	**40.3**	**57.7**	**9.6**	**45.7**
Respiratory System Average					**17.6**	**37.1**	**42.2**	**18.9**	**36.6**
Ophthalmology Average					**17.9**	**27.0**	**33.7**	**11.9**	**30.7**
Pain and Anesthesia Average					**27.8 [b]**	**34.0 [b]**	**38.0 [b]**	**31.7**	**36.6 [b]**
Immunomodulation Average					**13.1**	**33.1**	**36.3**	**16.8**	**39.6**
All Therapeutic Areas Average					**27.8**	**34.0**	**38.0**	**16.2**	**36.6] [c]**

NA = Not available

[a] This represents the therapeutic area or disease for which the duration estimates correspond to in the original source. We mapped these reported therapeutic areas and/or diseases to the therapeutic areas in this model.

[b] The figure is the All Therapeutic Areas average duration as no information was available for the therapeutic area and phase combination.

[c] This represents the average across all estimates in the table from Anti-infective through Immunomodulation therapeutic areas.

As can be observed from Table 2, there is overlap between successive stages of clinical development. For example, sponsors begin Phase 2 studies on a larger cohort of patients with more diverse conditions when initial safety and dosing results from Phase 1 studies are available even if those studies may not be fully complete. Thus, even though a Phase 1 study is estimated to last around 27.8 months on average across all therapeutic areas, a sponsor may begin a Phase 2 study on average 16.6 months after initiating the associated Phase 1 study.

5.3 AVERAGE NUMBER OF PATIENTS ENROLLED PER TRIAL

Number of patients enrolled in a study is the largest single factor driving study costs (Moore, et al., 2020). We used three databases (Medidata, clinicaltrials.gov, and FDA DASH), of which FDA DASH and Medidata are non-public, to estimate the average number of patients enrolled per trial by therapeutic area and phase (Table 4). The databases used cover different periods and vary in sample size, i.e., number of studies included. Ideally, the average number of patients enrolled estimate should be based on recent trials (preferably in the last 5 years) conducted in support of an NDA or BLA submission to FDA and rely on a large number of trials for each therapeutic area. None of the three databases satisfy these criteria fully. For example, Medidata database includes large number of studies, but it covers studies from 2004 through 2012 and includes trials that are not conducted in support of an NDA or BLA application to FDA. Similar to Medidata, clinicaltrials.gov database has a large number of studies from 2014 through June 2020 but also includes those that are not conducted in support of an NDA or BLA. On the other hand, FDA DASH database includes information from more recent trials (2007 through 2017) that are conducted in support of an FDA application but has fewer studies[8] and does not include data on Phase 1 or Phase 4 trials or those trials that failed. Thus, we used all three databases to calculate the weighted average number of patients enrolled by therapeutic area and phase where the weights are the number of studies in each database.

Given the proprietary nature of information used, Table 4 only depicts the weighted mean number of patients per trial by therapeutic area estimated, where the weights are the number of studies in each data source relative to the total number of studies across all sources.

From Table 4, the weighted average number of patients per trial across different therapeutic areas are highly variable. For Phase 1, the weighted average ranges from 31 patients for hematology to 121 for ophthalmology trials; 133 for dermatology to 323 immunomodulation trials for Phase 2; 233 for hematology to 1,209 for pain and anesthesia trials for Phase 3; and 261 for oncology to 1,430 for anti-infective trials for Phase 4. Across all therapeutic areas, the weighted average number of patients enrolled per trial is 51 for Phase 1, 235 for Phase 2, 630 for Phase 3, and 708 for Phase 4.

[8] DASH specifically captures "level of evidence" studies: pivotal and supportive studies used to support the regulatory approval of the drug. This is often a subset of the total number of trials conducted and/or submitted in the marketing application. One can then argue that since FDA DASH captures "real" applications and is a better reflection of the types of studies included in applications, then having fewer studies is not necessarily a weakness/limitation.

Table 4. Average Number of Patients per Trial, by Therapeutic Area

Therapeutic Area	Phase	Weighted Average Number of Patients per Trial
Anti-Infective	Phase 1	69
	Phase 2	243
	Phase 3	575
	Phase 4	1,430
Cardiovascular	Phase 1	42
	Phase 2	189
	Phase 3	1,151
	Phase 4	508
Central Nervous System	Phase 1	44
	Phase 2	243
	Phase 3	529
	Phase 4	356
Dermatology	Phase 1	106
	Phase 2	133
	Phase 3	568
	Phase 4	850
Endocrine	Phase 1	38
	Phase 2	225
	Phase 3	414
	Phase 4	482
Gastrointestinal	Phase 1	38
	Phase 2	292
	Phase 3	496
	Phase 4	1,344
Genitourinary System	Phase 1	50
	Phase 2	323
	Phase 3	546
	Phase 4	410
Hematology	Phase 1	31
	Phase 2	134
	Phase 3	233
	Phase 4	411
Immunomodulation	Phase 1	55
	Phase 2	323
	Phase 3	309
	Phase 4	383
Oncology	Phase 1	58
	Phase 2	137
	Phase 3	293
	Phase 4	261
Ophthalmology	Phase 1	121
	Phase 2	299
	Phase 3	876
	Phase 4	413
Pain and Anesthesia	Phase 1	36
	Phase 2	270
	Phase 3	1,209

Therapeutic Area	Phase	Weighted Average Number of Patients per Trial
	Phase 4	280
Respiratory System	Phase 1	49
	Phase 2	203
	Phase 3	516
	Phase 4	1,159
All Therapeutic Areas	**Phase 1**	**51**
	Phase 2	**235**
	Phase 3	**630**
	Phase 4	**708**

Further, within several therapeutic area and phase combinations, the variation across the average number of patients reported in the different databases is also significant. For example, the average number of patients in Phase 3 cardiovascular trials in FDA DASH is over nine times larger than that estimated from clinicaltrials.gov and over five times larger than that estimated from Medidata. However, there are a few therapeutic area and phase combinations for which this variation is minimal, such as Phase 2 and Phase 3 dermatology trials.

5.4 AVERAGE NUMBER OF TRIALS CONDUCTED IN SUPPORT OF AN FDA NDA/BLA APPLICATION

Sponsors indicate whether a trial is associated with an IND when they register it in clinicaltrials.gov. However, this information is only available to the National Institutes of Health (NIH) and the FDA, not to the general public. Thus, we requested a custom data pull from FDA CDER to estimate the average number of trials per IND application. FDA's internal tracking system allows drug application reviewers to select from over 800 IND Division Class Codes (Tier 3), which are mapped onto 43 broader (Tier 1) division class categories. We mapped our therapeutic areas to these 43 FDA categories and FDA CDER compiled the number of INDs and IND-linked clinical trials by these therapeutic areas and phase. Next, FDA CDER calculated the average number of trials by therapeutic area and phase by dividing the clinical trial counts for a given phase and therapeutic area by the unique IND counts for the same phase and therapeutic area. FDA CDER's (2019d) estimates are provided in Table 5.

From Table 5, the average number of trials conducted in support of an FDA application for a new drug is 1.71 for Phase 1, 1.52 for Phase 2, 2.66 for Phase 3, and 1.64 for Phase 4 across all therapeutic areas. For most therapeutic areas, sponsors conduct more than the two required Phase 3 trials with some running over four (endocrine) Phase 3 trials.

Table 5. Average Number of Trials Conducted in Support of an FDA NDA/BLA Application, by Therapeutic Area and Phase

Therapeutic Area	Phase 1	Phase 2	Phase 3	Phase 4
Anti-Infective	2.06	1.55	2.41	1.55
Cardiovascular	1.65	1.43	2.40	1.99
Central Nervous System	1.77	1.36	2.83	1.56
Dermatology	1.74	1.69	2.56	1.42
Endocrine	2.11	1.67	4.25	1.91
Gastrointestinal	1.81	1.41	2.46	1.61
Genitourinary System	1.58	1.34	1.47	1.00
Hematology	1.62	1.63	2.37	1.59
Immunomodulation	1.96	1.57	3.09	1.86
Oncology	1.36	1.34	1.63	1.29
Ophthalmology	1.23	1.57	2.47	1.83
Pain and Anesthesia	1.90	1.65	2.92	1.49
Respiratory System	1.46	1.55	3.75	2.22
All Therapeutic Areas	**1.71**	**1.52**	**2.66**	**1.64**

Source: FDA CDER, (2019d)
[a] Data are current as of 7/23/2019.
[b] Excludes INDs received by CDER prior to the establishment of clinicaltrials.gov.
[c] Excludes trials not conducted under an IND.
[d] Excludes trials not registered with clinicaltrials.gov.
[e] Excludes trials associated with INDs not having a Division Classification Code.
[f] Excludes trials associated with INDs having a Division Classification Code that was not mapped to any of the therapeutic areas included in this model
[g] Division Classification Codes have not undergone quality control to ensure accuracy.
[h] The figures are calculated by dividing the number of trials for a given therapeutic area and phase by a distinct count of IND(s) associated with the corresponding cohort of trials (within the same therapeutic area and phase).

5.5 AVERAGE COST PER PATIENT

The total cost of a clinical trial for a given phase and therapeutic area, C_{total}, includes study-level costs (such as institutional review board approvals and source data verification costs), C_{study}, patient-level costs (such as recruitment and clinical procedure costs), $C_{patient}$, and site-level costs (such as monitoring and project management), C_{site} (Sertkaya, et al., 2016), i.e.:

$$C_{total} = C_{study} + C_{patient} + C_{site} \quad (9)$$

Then, the average cost per-patient, CPP, can be calculated by dividing the total cost of a clinical trial C_{total}, by the number of patients, $n_{patient}$, enrolled in that trial, i.e.:

$$CPP = \frac{C_{total}}{n_{patient}} \quad (10)$$

We used three different data sources to estimate the average cost per patient. Two of the data sources (Cutting Edge and Medidata) included data on total clinical trial costs and the number of patients enrolled which allowed us to directly estimate the average cost per patient

using the above equation. The third source, IQVIA, only contained information on patient-level costs, which comprise between 10 to 70 percent of total trial costs depending on therapeutic area and phase according to information available from the Medidata database. For comparability, we adjusted the reported IQVIA patient-level costs by these percentages. For example, if IQVIA reported a patient level cost of $10,000 for a Phase 1 study and patient-level costs were estimated to be around 20 percent of total costs in Medidata for that therapeutic area, we estimated the IQVIA average cost per patient at $50,000 (= $10,000 ÷ 0.20). The approach assumes that the shares of study, patient, and site costs for IQVIA are equivalent to those in Medidata. Due to the proprietary nature of these databases, we only present the weighted average cost per patient estimates by therapeutic area and phase in Table 6, where the weights are the number of studies in each database. As expected, the average cost per patient varies significantly by therapeutic area; $19,399 (anti-infective) to $349,363 (hematology) for Phase 1, $41,323 (cardiovascular) to $100,554 (hematology) for Phase 2, $30,001 (anti-infective) to $118,473 (hematology) for Phase 3, and $13,814 (anti-infective) to $56,824 (endocrine) for Phase 4. Across all therapeutic areas, the average cost per patient is $81,338 for Phase 1, $58,618 for Phase 2, $53,180 for Phase 3, and $35,190 for Phase 4 trials.

Table 6. Average Per-patient Costs (in 2018 $), by Therapeutic Area and Phase

Therapeutic Area	Phase	Weighted Average
Anti-Infective	Phase 1	$19,399
	Phase 2	$59,289
	Phase 3	$30,001
	Phase 4	$13,814
Cardiovascular	Phase 1	$59,456
	Phase 2	$41,323
	Phase 3	$33,084
	Phase 4	$33,915
Central Nervous System	Phase 1	$87,390
	Phase 2	$48,767
	Phase 3	$39,612
	Phase 4	$34,956
Dermatology	Phase 1	$35,450
	Phase 2	$66,661
	Phase 3	$48,587
	Phase 4	$33,102
Endocrine	Phase 1	$85,463
	Phase 2	$51,556
	Phase 3	$48,753
	Phase 4	$56,824
Gastrointestinal	Phase 1	$61,848
	Phase 2	$63,590
	Phase 3	$47,656
	Phase 4	$52,746
Genitourinary System	Phase 1	$53,770
	Phase 2	$45,781
	Phase 3	$38,930

Therapeutic Area	Phase	Weighted Average
	Phase 4	$16,699
Hematology [a]	Phase 1	$349,363
	Phase 2	$100,554
	Phase 3	$118,473
	Phase 4	$41,958
Immunomodulation	Phase 1	$63,471
	Phase 2	$47,897
	Phase 3	$54,909
	Phase 4	$30,246
Oncology	Phase 1	$103,344
	Phase 2	$78,753
	Phase 3	$93,145
	Phase 4	$23,515
Ophthalmology	Phase 1	$50,999
	Phase 2	$48,438
	Phase 3	$79,933
	Phase 4	$24,022
Pain and Anesthesia	Phase 1	$90,370
	Phase 2	$77,726
	Phase 3	$60,751
	Phase 4	$41,573
Respiratory System	Phase 1	$44,330
	Phase 2	$43,563
	Phase 3	$46,764
	Phase 4	$18,987
All Therapeutic Areas	**Phase 1**	**$81,338**
	Phase 2	**$58,618**
	Phase 3	**$53,180**
	Phase 4	**$35,190**

[a] The representativeness of this category is highly limited due to small sample sizes and the types of indications covered in the included trials.

5.6 PHASE TRANSITION SUCCESS PROBABILITIES

The phase transition success probability parameter represents the probability of a sponsor successfully moving from one stage of drug development to the next. If, for example, out of 100 new drug candidates that make it to Phase 1, 30 successfully proceed to Phase 2, then the phase transition probability from Phase 1 to Phase 2 is 30 percent. We used published studies to estimate the average phase transition success probabilities (Table 7). Across all therapeutic areas, successfully transitioning from Phase 2 to Phase 3 generally has the lowest likelihood at 35.9 percent (ranging from 27.4 percent for respiratory system to 56.6 percent for hematology). Getting approval from the FDA for a new drug that has cleared Phase 3 has on average 88.3 percent likelihood across all therapeutic areas. Further, only 8.5 percent (= 0.68 × 0.602 × 0.359 × 0.655 × 0.883) of new drug candidates successfully move from non-clinical development to market. However, as the drug candidate successfully clears each successive development stage, the odds of making it to market improve. As expected, there is variation in

this likelihood across therapeutic areas with hematology drugs having the highest likelihood at 17.8 percent and oncology drugs having the lowest likelihood at 4.1 percent (not shown).

Table 7. Transition Success Probabilities, by Therapeutic Area and Phase

Data Source	Time Period	Therapeutic Area	Therapeutic Area in the Original Source [a]	Other Classification	Nonclinical to Phase 1	Phase 1 to Phase 2	Phase 2 to Phase 3	Phase 3 to FDA Review	FDA Review to Approval
Wong et al (2019)	2000-2015	Anti-Infective	Infectious Disease	NA	NA	70.1%	58.3%	NA	NA
DiMasi et al (2010)	1993-2004		Systemic Anti-infective	NA	NA	58.2%	52.2%	78.6%	100.0%
BiomedTracker (2016)	2006-2015		Infectious Disease	NA	NA	69.5%	42.7%	72.7%	88.7%
BiomedTracker, 2017 [c]	2010-2016		Infectious Disease	NA	NA	NA	45.0%	71.0%	NA
Wong et al (2019)	2000-2015	Cardiovascular	Cardiovascular	NA	NA	73.3%	65.7%	NA	NA
DiMasi et al (2010)	1993-2004		Cardiovascular	NA	NA	62.9%	32.4%	64.3%	66.7%
BiomedTracker (2016)	2006-2015		Cardiovascular	NA	NA	58.9%	24.1%	55.5%	84.2%
BiomedTracker, 2017 [c]	2010-2016		Cardiovascular	NA	NA	NA	26.0%	53.0%	NA
Wong et al (2019)	2000-2015	Central Nervous System	Central Nervous System	NA	NA	73.2%	51.9%	NA	NA
DiMasi et al (2010)	1993-2004		Central Nervous System	NA	NA	59.6%	33.0%	46.4%	90.0%
BiomedTracker (2016)	2006-2015		Neurology	NA	NA	59.1%	29.7%	57.4%	83.2%
BiomedTracker (2016)	2006-2015		Psychiatry	NA	NA	53.9%	23.7%	55.7%	87.9%
BiomedTracker, 2017 [c]	2010-2016		Neurology	NA	NA	NA	33.0%	60.0%	NA
BiomedTracker, 2017 [c]	2010-2016		Psychiatry	NA	NA	NA	27.0%	60.0%	NA
Wong et al (2019)	2000-2015	Endocrine	Metabolic Diseases	NA	NA	76.2%	59.7%	NA	NA
Wong et al (2019)	2000-2015		Endocrinology	NA	NA	76.2%	59.7%	NA	NA
DiMasi et al (2010)	1993-2004		Gastroenterology/Metabolism	NA	NA	67.5%	34.9%	50.0%	80.0%
BiomedTracker (2016)	2006-2015		Metabolic Diseases	NA	NA	61.1%	45.2%	71.4%	77.8%
BiomedTracker (2016)	2006-2015		Endocrinology	NA	NA	58.9%	40.1%	65.0%	86.0%
BiomedTracker, 2017 [c]	2010-2016		Endocrinology	NA	NA	NA	38.0%	69.0%	NA
DiMasi et al (2010)	1993-2004	Gastrointestinal	Gastroenterology/Metabolism	NA	NA	67.5%	34.9%	50.0%	80.0%
BiomedTracker (2016)	2006-2015		Gastroenterology	NA	NA	75.6%	35.7%	60.6%	92.3%
Wong et al (2019)	2000-2015	Genitourinary System	Genitourinary	NA	NA	68.7%	57.1%	NA	NA
BiomedTracker (2016)	2006-2015		Urology	NA	NA	57.1%	32.7%	71.4%	85.7%
BiomedTracker (2016)	2006-2015	Hematology	Hematology	NA	NA	73.3%	56.6%	75.0%	84.0%
Wong et al (2019)	2000-2015	Immunomodulation	Autoimmune Diseases	NA	NA	69.8%	45.7%	NA	NA
Wong et al (2019)	2000-2015		Inflammation	NA	NA	69.8%	45.7%	NA	NA
DiMasi et al (2010)	1993-2004		Antineoplastic/immunologic	NA	NA	71.8%	49.0%	55.3%	100.0%
DiMasi et al (2010)	1993-2004		Musculoskeletal	NA	NA	72.4%	35.2%	80.0%	100.0%
BiomedTracker (2016)	2006-2015		Autoimmune Diseases	NA	NA	65.7%	31.7%	62.2%	86.0%
BiomedTracker, 2017	2010-2016		Autoimmune Diseases	NA	NA	NA	33.0%	64.0%	NA
Wong et al (2019)	2000-2015	Oncology	Oncology	NA	NA	57.6%	32.7%	NA	NA
DiMasi et al (2010)	1993-2004		Antineoplastic/immunologic	NA	NA	71.8%	49.0%	55.3%	100.0%

Data Source	Time Period	Therapeutic Area	Therapeutic Area in the Original Source [a]	Other Classification	Nonclinical to Phase 1	Phase 1 to Phase 2	Phase 2 to Phase 3	Phase 3 to FDA Review	FDA Review to Approval
BiomedTracker (2016)	2006-2015		Oncology	NA	NA	62.8%	24.6%	40.1%	82.4%
BiomedTracker (2016)	2006-2015		Solid Tumors	NA	NA	64.1%	23.0%	34.2%	79.6%
BiomedTracker (2016)	2006-2015		Hematological Cancers	NA	NA	61.8%	28.7%	52.6%	86.4%
BiomedTracker, 2017 [c]	2010-2016		Oncology	NA	NA	NA	27.0%	45.0%	NA
Pharma Intelligence, Informa, 2016 [c]	2011-2015		Oncology	NA	NA	59.0%	21.0%	38.0%	84.0%
Pharma Intelligence, Informa, 2016 [c]	2011-2015		Solid Tumors	NA	NA	57.0%	20.0%	32.0%	83.0%
Pharma Intelligence, Informa, 2016 [c]	2011-2015		Hematological Cancers	NA	NA	64.0%	26.0%	54.0%	84.0%
Pharma Intelligence, Informa, 2016 [c]	2011-2015		Oncology	NME	NA	56.0%	18.0%	36.0%	77.0%
Pharma Intelligence, Informa, 2016 [c]	2011-2015		Oncology	Large Molecule	NA	61.0%	25.0%	40.0%	93.0%
Wong et al (2019)	2000-2015	Ophthalmology	Ophthalmology	NA	NA	87.1%	60.7%	NA	NA
BiomedTracker (2016)	2006-2015		Ophthalmology	NA	NA	84.8%	44.6%	58.3%	77.5%
DiMasi et al (2010)	1993-2004	Respiratory System	Respiratory	NA	NA	72.5%	20.0%	85.7%	80.0%
BiomedTracker (2016)	2006-2015		Allergy	NA	NA	67.6%	32.5%	71.4%	93.8%
BiomedTracker (2016)	2006-2015		Respiratory	NA	NA	65.3%	29.1%	71.1%	94.6%
BiomedTracker, 2017 [c]	2010-2016		Respiratory	NA	NA	NA	28.0%	74.0%	NA
Wong et al (2019)	2000-2015	All Therapeutic Areas	Overall	NA	NA	66.4%	58.3%	NA	NA
DiMasi et al (2010)	1993-1998		Overall	NA	NA	67.0%	41.0%	63.0%	90.0%
DiMasi et al (2010)	1999-2004		Overall	NA	NA	64.0%	39.0%	66.0%	100.0%
DiMasi et al (2010)	1993-2004		Overall	Self-originated	NA	65.0%	40.0%	64.0%	93.0%
DiMasi et al (2010)	1993-2004		Overall	Licensed-in	NA	82.0%	56.0%	64.0%	93.0%
DiMasi et al (2010)	1993-2004		Overall	NA	NA	71.0%	45.0%	64.0%	93.0%
DiMasi et al (2010)	1993-2004		Overall	Small Molecule	NA	63.0%	38.0%	61.0%	91.0%
DiMasi et al (2010)	1993-2004		Overall	Large Molecule	NA	84.0%	53.0%	74.0%	96.0%
DiMasi et al (2010)	1995-2007		Overall	NA	NA	59.5%	35.5%	62.0%	90.4%
BiomedTracker (2016)	2006-2015		Overall	NA	NA	63.2%	30.7%	58.1%	85.3%
BiomedTracker (2016)	2006-2015		Overall	NME	NA	61.3%	26.5%	48.7%	78.0%
BiomedTracker (2016)	2006-2015		Overall	Large Molecule	NA	66.0%	34.4%	57.2%	88.4%
BiomedTracker (2016)	2006-2015		Overall	Non-NME	NA	70.1%	48.3%	73.9%	90.4%
BiomedTracker (2016)	2006-2015		Chronic High Prevalence Diseases	NA	NA	58.7%	27.7%	61.6%	87.2%
BiomedTracker (2016)	2006-2015		Rare Diseases	NA	NA	76.0%	50.6%	73.6%	89.2%
KMR Bernstein Analysis, 2016 [c]	2003-2007		Overall	NA	69.0%	54.0%	34.0%	70.0%	91.0%
KMR Bernstein Analysis, 2016 [c]	2005-2009		Overall	NA	64.0%	48.0%	25.0%	67.0%	83.0%
KMR Bernstein Analysis, 2016 [c]	2007-2011		Overall	NA	64.0%	44.0%	22.0%	65.0%	83.0%
KMR Bernstein Analysis, 2016 [c]	2007-2011		Overall	Small Molecule	61.0%	42.0%	18.0%	60.0%	85.0%

Data Source	Time Period	Therapeutic Area	Therapeutic Area in the Original Source [a]	Other Classification	Nonclinical to Phase 1	Phase 1 to Phase 2	Phase 2 to Phase 3	Phase 3 to FDA Review	FDA Review to Approval
KMR Bernstein Analysis, 2016 [c]	2007-2011		Overall	Large Molecule	75.0%	56.0%	44.0%	79.0%	79.0%
KMR Bernstein Analysis, 2016 [c]	2010-2014		Overall	NA	67.0%	44.0%	29.0%	69.0%	88.0%
KMR Bernstein Analysis, 2016 [c]	2010-2014		Overall	Small Molecule	62.0%	40.0%	24.0%	65.0%	90.0%
KMR Bernstein Analysis, 2016 [c]	2010-2014		Overall	Large Molecule	76.0%	53.0%	40.0%	79.0%	86.0%
KMR Bernstein Analysis, 2016 [c]	2011-2015		Overall	NA	68.0%	45.0%	33.0%	77.0%	92.0%
KMR Bernstein Analysis, 2016 [c]	2011-2015		Overall	Small Molecule	63.0%	41.0%	30.0%	72.0%	92.0%
KMR Bernstein Analysis, 2016 [c]	2011-2015		Overall	Large Molecule	79.0%	52.0%	39.0%	88.0%	93.0%
BiomedTracker, 2017 [c]	2011		Overall	NA	NA	64.0%	32.0%	60.0%	83.0%
BiomedTracker, 2017 [c]	2012		Overall	NA	NA	65.0%	33.0%	61.0%	85.0%
BiomedTracker, 2017 [c]	2013		Overall	NA	NA	64.0%	32.0%	60.0%	86.0%
BiomedTracker, 2017 [c]	2014		Overall	NA	NA	65.0%	33.0%	62.0%	87.0%
BiomedTracker, 2017 [c]	2015		Overall	NA	NA	64.0%	32.0%	61.0%	87.0%
BiomedTracker, 2017 [c]	2016		Overall	NA	NA	65.0%	33.0%	60.0%	88.0%
BiomedTracker, 2017 [c]	2016		Overall	NME	NA	62.0%	28.0%	51.0%	83.0%
Anti-Infective Average					**68.0% [b]**	**65.9%**	**49.6%**	**74.1%**	**94.4%**
Cardiovascular Average						**65.0%**	**37.1%**	**57.6%**	**75.5%**
Central Nervous System Average						**61.5%**	**33.1%**	**55.9%**	**87.0%**
Dermatology Average						**60.2% [b]**	**35.9% [b]**	**65.5% [b]**	**88.3% [b]**
Endocrine Average						**68.0%**	**46.3%**	**63.9%**	**81.3%**
Gastrointestinal Average						**71.6%**	**35.3%**	**55.3%**	**86.2%**
Genitourinary System Average						**62.9%**	**44.9%**	**71.4%**	**85.7%**
Hematology Average						**73.3%**	**56.6%**	**75.0%**	**84.0%**
Oncology Average						**61.5%**	**26.8%**	**42.7%**	**85.5%**
Respiratory System Average						**68.5%**	**27.4%**	**75.6%**	**89.5%**
Ophthalmology Average						**86.0%**	**52.7%**	**58.3%**	**77.5%**
Pain and Anesthesia Average						**60.2% [b]**	**35.9% [b]**	**65.5% [b]**	**88.3% [b]**
Immunomodulation Average						**69.9%**	**40.1%**	**65.4%**	**95.3%**
All Therapeutic Areas Average						**60.2%**	**35.9%**	**65.5%**	**88.3%**

NA = Not available/Not applicable

[a] This represents the therapeutic area or disease for which the duration estimates correspond to in the original source. We mapped these reported therapeutic areas and/or diseases to the therapeutic areas in this model.

[b] The figure is the All Therapeutic Areas average transition probability as no information was available for the therapeutic area and phase-to-phase combination.

[c] From PAREXEL's biopharmaceutical R&D statistical yearbook (PAREXEL International Corp., 2017).

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 drug 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 several 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. Table 8 presents the different OCOC estimates available from the published literature. For the model, we used 11 percent as the OCOC for drug development projects, which is the average of figures reported for the biopharmaceutical industry as a whole.

Table 8. Published Estimates of Opportunity Cost of Capital

Data Source	Sub-Sector	Firm Size	Study Period	Sample Size	Opportunity Cost of Capital
DiMasi et al, (2016)	All	All	2000	NA	11.8%
			2005	NA	10.8%
			2010	NA	9.4%
DiMasi et al, (2003)	All	All	2000	NA	11.9%
Damodaran, (2018)	Large Molecule	All	2018	459	9.2%
	Small Molecule	All	2018	185	8.1%
Damodaran, (2019)	Large Molecule	All	2019	481	10.5%
	Small Molecule	All	2019	237	10.5%
Paul et al, (2010)	All	All	2007	NA	11.0%
Harrington, (2012)	Small Molecule	All	2001-2005	31	9.8%
		Large	2001-2005	22	9.6%
		Small	2001-2005	9	10.6%
	Large Molecule	All	2001-2005	26	14.2%
		Large	2001-2005	17	14.1%
		Small	2001-2005	9	14.5%
	Small Molecule	All	2006-2008	28	9.3%
		Large	2006-2008	21	9.5%

Data Source	Sub-Sector	Firm Size	Study Period	Sample Size	Opportunity Cost of Capital
		Small	2006-2008	7	8.6%
	Large Molecule	All	2006-2008	29	11.8%
		Large	2006-2008	14	10.2%
		Small	2006-2008	15	13.2%
Average	**Large Molecule**	**Large**			**12.2%**
		Small			**13.9%**
		All			**11.4%**
	Small Molecule	**Large**			**9.6%**
		Small			**9.6%**
		All			**9.4%**
	All	**Large**			**NA**
		Small			**NA**
		All [a]			**11.0%**

NA = Not available

[a] Estimate used in this model.

5.8 OUT-OF-POCKET COST ESTIMATES

We calculated the total out-of-pocket cost by phase and therapeutic area as the product of per-patient cost (CPP), average number of patients enrolled per trial, and the average number of trials. The out-of-pocket cost for the FDA BLA/NDA review and approval was estimated at $2.6 million, the published FDA fee for an application requiring clinical data for fiscal year 2019 that spans October 1, 2018 through September 30, 2019 (Federal Register, 2018).

To estimate non-clinical cost, we adopted the approach by DiMasi et al (2016). There are no published data on non-clinical costs per drug candidate. Pharmaceutical companies have long claimed that it is difficult to attribute non-clinical R&D expenses to drug candidate compounds. In their 2016 study, DiMasi et al. estimated the ratio, R, of preclinical to clinical expenditures based on aggregated data on preclinical spending and assumptions around the duration of preclinical testing. Based on the reported amounts in Figure 2 of that study, they estimated the preclinical and clinical costs at $430 million and $965 million in 2013 dollars per approved drug, which translates to a ratio of 44.6 percent (DiMasi, et al., 2016). These estimates were based on data voluntarily submitted by anonymous biopharmaceutical companies as well as proprietary databases. The specifics of how they calculated this ratio is neither fully detailed in their study nor is available in other studies that are in the public domain. Thus, similar to other studies on this topic, we relied on the same reported ratio, 44.6 percent, to estimate non-clinical out of pocket costs per approved drug, which were then translated to a cost per drug candidate basis using the estimated aggregate mean success to approval rates by phase. More specifically, given that the estimated Phase 1, 2, and 3 costs are C_1, C_2, and C_3) and the estimated probability of approval from a given phase, i, is P_i, then the expected non-clinical stage cost, $E(C_{non-clinical})$, per approved drug was calculated from equation (1) as:

$$E(C_{non-clinical}) = 0.446 \times [E(C_1) + E(C_2) + E(C_3)] = 0.446 \times \left[\frac{C_1}{P_1} + \frac{C_2}{P_2} + \frac{C_3}{P_3}\right] \quad (11)$$

Then, using equations (1) and (11), the non-clinical cost per drug candidate was calculated as:

$$C_{non-clinical} = E(C_{non-clinical}) \times P_{non-clinical} \quad (12)$$

Given the sizable impact of non-clinical cost on overall cost of drug development, we also conducted a sensitivity analysis by varying this value +/-10 percent (Table 9). As can be observed from the table, the change in this ratio results in a proportionate change in expected capitalized cost estimate but a less than proportionate change in mean out-of-pocket cost estimate.

Table 9. Sensitivity Analysis of Varying Assumptions on Non-clinical to Clinical R&D Ratio, R, on Overall Cost Estimates

Scenario	Out-of-pocket Cost (in $ 2018 Million) [a]	Expected Cost (in $ 2018 Million) [b]	Expected Capitalized Cost (in $ 2018 Million) [c]
Base Case: R = 44.6%	$172.7	$515.8	$879.3
Scenario 1: R = 34.6%	$170.0	$484.6	$800.0
Scenario 2: R = 54.6%	$175.3	$547.1	$958.7
Scenario 3: R ~ *N*(44.6%, 10%)	$172.7 ($132.8 – $199.5)	$515.8 ($322.0 – $778.0)	$879.3 ($407.0 – $1,348.0)

[a] Represents the cash outlay not adjusted for the cost of capital or failures.
[b] Represents R&D cost after adjusting for the cost of failures computed as the total out-of-pocket cost divided by the aggregate transition success probability; includes cost of failures but not the cost of capital.
[c] Represents costs inclusive of failure and capital costs.

5.9 RESULTS

5.10 BASELINE DEVELOPMENT COST ESTIMATES

According to published studies that rely on proprietary data, the cost of drug development could range from $314 million to $2.8 billion (in 2018 dollars) depending on the therapeutic area, the cost of capital or phase transition success rate assumptions used in the modeling (DiMasi, et al., 2003; Jayasundara, et al., 2019; Mestre-Ferrandiz, et al., 2012; Adams & Brantner, 2006; Adams & Brantner, 2010; DiMasi & Grabowski, 2007; DiMasi, et al., 2004; DiMasi, et al., 2016; Paul, et al., 2010). Recent studies that have used publicly available data (mainly data reported by biopharmaceutical companies to the Securities and Exchange Commission in their annual 10-K and Quarterly 10-Q filings) report cost figures that range from $734 million for cancer (Prasad & Mailankody, 2017) to $4,461.2 million for antineoplastic and immunomodulating agents (Wouters, et al., 2020) (see Table 10).

Our analysis suggests that the average out-of-pocket cost of developing a new drug is around $131.8 million before conducting post-approval studies, and approximately $172.7 million when post-approval studies are accounted for (see Table 11). Of those costs inclusive of post-approval Phase 4 studies, 7 percent is non-clinical stage related, 68 percent is clinical stage (i.e., Phase 1, 2, and 3) related, 2 percent is review phase, and the remaining 24 percent is associated with post-approval stage, which includes Phase 3 follow-up studies, where applicable, and Phase 4 post-marketing studies. When capitalized to account for cost of capital and after accounting for the costs of failures, expected capitalized average development cost for new drug development is approximately $844.6 million before conducting post-approval studies and $879.3 million after conducting them. These development costs vary widely depending on therapeutic area as shown in Table 11. At one end of the spectrum are anti-infective drugs that cost about a third of this estimate ($378.7 million including post approval study costs) and at the other end are pain and anesthesia drugs that are more than four times as costly to develop ($1,756.2 million including Phase 4 costs).

Table 10. Recent Published Estimates of Cost of Drug Development

Source	N	Cost of Capital	Type	Average Cost (in 2018 $)
Prasad & Mailankody (2017)	10	7%	Cancer	$734.0 million (95% CI: $342.6 to $1,125.8 million) [a]
Wouters, et al. (2020)	20	10.5%	Antineoplastic & Immunomodulating Agents	$4,461.2 million (95% CI: $3,114.0 to $6,001.3 million)
	15		Alimentary Tract and Metabolism	$1,430.3 million (95% CI: $920.8 to $2,078.7 million)
	8		Nervous System	$1,076.9 million (95% CI: $508.7 to $1,847.1 million)
	5		Anti-infectives for Systemic Use	$1,297.2 million (95% CI: $672.5 to $1,858.5 million)
	4		Dermatologicals	$1,998.3 million [b]
	3		Cardiovascular System	$1,152.4 million [b]
	3		Musculoskeletal System	$937.3 million [b]
	2		Blood and Blood-forming Organs	$793.0 million [b]
	2		Sensory Organs	$1,302.8 million [b]
	1		Other	$1,121.0 million [b]
	63		Overall	$1,335.9 million (95% CI: $1,042.5 to-$1,637.5 million)

CI = Confidence interval

[a] The reported study estimates were in 2017 dollars. We used the Medical Care Price Index to inflate 2017 to 2018 dollars.

[b] Study authors did not calculate bootstrapped confidence intervals for those therapeutic areas with less than n = 5 samples.

Table 11. Average Cost of Developing a Drug for the U.S. Market (in Million $ 2018)

Parameter	Phase	Anti-Infective	Cardiovascular	Central Nervous System	Dermatology	Endocrine	Gastrointestinal	Genitourinary System	Hematology	Oncology	Respiratory System	Ophthalmology	Pain and Anesthesia	Immunomodulation	All Therapeutic Areas
Out-of-Pocket Costs (in Million $ 2018) [b]	Non-clinical	$9.4	$10.1	$8.7	$9.3	$14.2	$11.4	$7.7	$17.9	$7.0	$9.0	$32.0	$22.2	$11.6	$11.8
		9%	7%	8%	6%	8%	5%	11%	12%	8%	5%	12%	7%	10%	7%
	Clinical Phases	$66.7	$106.6	$82.3	$92.0	$112.0	$88.7	$55.3	$101.3	$60.3	$107.4	$203.4	$255.1	$83.5	$117.4
		61%	69%	73%	64%	62%	41%	76%	66%	71%	64%	79%	86%	70%	68%
	Phase 1	$2.8	$4.2	$6.8	$6.5	$6.8	$4.3	$4.2	$17.3	$8.1	$3.2	$7.6	$6.1	$6.8	$7.1
		3%	3%	6%	5%	4%	2%	6%	11%	10%	2%	3%	2%	6%	4%
	Phase 2	$22.3	$11.2	$16.1	$14.9	$19.4	$26.2	$19.8	$22.1	$14.5	$13.7	$22.8	$34.6	$24.3	$21.0
		20%	7%	14%	10%	11%	12%	27%	14%	17%	8%	9%	12%	20%	12%
	Phase 3	$41.6	$91.2	$59.4	$70.6	$85.8	$58.1	$31.3	$61.9	$37.7	$90.5	$173.0	$214.4	$52.4	$89.3
		38%	59%	53%	49%	47%	27%	43%	40%	45%	54%	68%	72%	44%	52%
	FDA Submission	$2.6	$2.6	$2.6	$2.6	$2.6	$2.6	$2.6	$2.6	$2.6	$2.6	$2.6	$2.6	$2.6	$2.6
		2%	2%	2%	2%	1%	1%	4%	2%	3%	2%	1%	1%	2%	1%
	Post-approval Phase	$30.7	$34.2	$19.4	$39.8	$52.3	$114.0	$6.9	$31.1	$14.8	$48.8	$18.2	$17.4	$21.5	$40.9
		28%	22%	17%	28%	29%	53%	9%	20%	17%	29%	7%	6%	18%	24%
	Total (without Phase 4 costs)	**$78.7**	**$119.3**	**$93.6**	**$103.9**	**$128.9**	**$102.7**	**$65.7**	**$121.8**	**$69.9**	**$118.9**	**$238.0**	**$279.9**	**$97.7**	**$131.8**
		72%	**78%**	**83%**	**72%**	**71%**	**47%**	**91%**	**80%**	**83%**	**71%**	**93%**	**94%**	**82%**	**76%**
	Total (with Phase 4 costs)	**$109.4**	**$153.5**	**$113.0**	**$143.8**	**$181.2**	**$216.7**	**$72.5**	**$152.9**	**$84.7**	**$167.8**	**$256.2**	**$297.2**	**$119.3**	**$172.7**
		100%	**100%**	**100%**	**100%**	**100%**	**100%**	**100%**	**100%**	**100%**	**100%**	**100%**	**100%**	**100%**	**100%**
Expected Out-of-Pocket Costs (in Million $ 2018) [c]	Non-clinical	$60.6	$142.3	$129.7	$109.6	$128.3	$139.8	$65.8	$100.9	$171.7	$103.8	$229.9	$261.1	$98.2	$139.1
		24%	27%	28%	26%	26%	24%	27%	26%	29%	25%	29%	29%	27%	27%
	Clinical Phases	$136.1	$319.2	$291.1	$246.1	$287.8	$313.7	$147.8	$226.4	$385.4	$233.0	$515.9	$585.9	$220.4	$312.2
		54%	61%	63%	59%	59%	53%	61%	59%	65%	57%	66%	66%	61%	61%
	Phase 1	$12.1	$39.7	$69.0	$52.3	$41.5	$35.6	$24.5	$66.2	$134.2	$25.0	$37.2	$49.0	$39.1	$57.1
		5%	8%	15%	12%	8%	6%	10%	17%	23%	6%	5%	6%	11%	11%
	Phase 2	$64.5	$69.6	$100.0	$71.8	$80.9	$156.1	$72.2	$61.9	$148.0	$74.2	$95.8	$166.5	$97.2	$100.9
		26%	13%	22%	17%	16%	26%	30%	16%	25%	18%	12%	19%	27%	20%
	Phase 3	$59.5	$209.9	$122.1	$121.9	$165.4	$122.0	$51.1	$98.3	$103.3	$133.8	$383.0	$370.4	$84.1	$154.3
		24%	40%	26%	29%	34%	21%	21%	26%	17%	33%	49%	42%	23%	30%

Parameter	Phase	Anti-Infective	Cardiovascular	Central Nervous System	Dermatology	Endocrine	Gastrointestinal	Genitourinary System	Hematology	Oncology	Respiratory System	Ophthalmology	Pain and Anesthesia	Immunomodulation	All Therapeutic Areas
	FDA Submission	$23.6	$23.6	$23.6	$23.6	$23.6	$23.6	$23.6	$23.6	$23.6	$23.6	$23.6	$23.6	$23.6	$23.6
		9%	5%	5%	6%	5%	4%	10%	6%	4%	6%	3%	3%	6%	5%
	Post-approval Phase	$30.7	$34.2	$19.4	$39.8	$52.3	$114.0	$6.9	$31.1	$14.8	$48.8	$18.2	$17.4	$21.5	$40.9
		12%	7%	4%	10%	11%	19%	3%	8%	2%	12%	2%	2%	6%	8%
	Total (without Phase 4 costs)	**$220.3**	**$485.1**	**$444.3**	**$379.3**	**$439.7**	**$477.1**	**$237.2**	**$350.8**	**$580.7**	**$360.5**	**$769.4**	**$870.6**	**$342.1**	**$474.9**
		88%	**93%**	**96%**	**90%**	**89%**	**81%**	**97%**	**92%**	**98%**	**88%**	**98%**	**98%**	**94%**	**92%**
	Total (with Phase 4 costs)	**$251.0**	**$519.3**	**$463.7**	**$419.1**	**$492.0**	**$591.1**	**$244.0**	**$381.9**	**$595.5**	**$409.3**	**$787.6**	**$887.9**	**$363.7**	**$515.8**
		100%	**100%**	**100%**	**100%**	**100%**	**100%**	**100%**	**100%**	**100%**	**100%**	**100%**	**100%**	**100%**	**100%**
Capitalized Out-of-pocket Costs to Date of Launch (in Million $ 2018) [d]	Non-clinical	$21.1	$25.9	$24.2	$22.8	$32.5	$29.5	$16.8	$50.5	$20.3	$23.1	$68.4	$65.0	$27.0	$30.1
		15%	13%	15%	13%	14%	12%	16%	21%	16%	11%	20%	14%	16%	13%
	Clinical Phases	$89.3	$145.2	$122.0	$120.0	$152.5	$124.9	$77.7	$157.6	$88.8	$146.2	$251.6	$384.9	$117.1	$158.7
		64%	72%	74%	67%	66%	49%	75%	66%	72%	68%	74%	82%	71%	70%
	Phase 1	$4.9	$8.6	$15.0	$12.2	$12.6	$8.4	$7.5	$37.9	$17.5	$6.5	$13.0	$13.7	$12.9	$13.8
		3%	4%	9%	7%	5%	3%	7%	16%	14%	3%	4%	3%	8%	6%
	Phase 2	$34.0	$19.4	$29.0	$23.3	$31.3	$43.2	$31.0	$40.4	$25.4	$23.6	$33.8	$64.6	$39.0	$34.0
		24%	10%	17%	13%	13%	17%	30%	17%	21%	11%	10%	14%	24%	15%
	Phase 3	$50.5	$117.2	$78.1	$84.4	$108.6	$73.3	$39.2	$79.4	$45.8	$116.0	$204.9	$306.6	$65.2	$110.9
		36%	58%	47%	47%	47%	29%	38%	33%	37%	54%	60%	66%	40%	49%
	FDA Submission	$2.8	$2.8	$2.9	$2.7	$2.8	$2.8	$2.8	$2.8	$2.7	$2.8	$2.7	$3.0	$2.8	$2.8
		2%	1%	2%	2%	1%	1%	3%	1%	2%	1%	1%	1%	2%	1%
	Post-approval Phase	$25.8	$28.9	$16.6	$33.9	$45.0	$96.9	$6.0	$26.7	$12.1	$41.5	$15.9	$14.8	$18.1	$34.7
		19%	14%	10%	19%	19%	38%	6%	11%	10%	19%	5%	3%	11%	15%
	Total (without Phase 4 costs)	**$113.2**	**$173.9**	**$149.1**	**$145.5**	**$187.8**	**$157.2**	**$97.3**	**$210.9**	**$111.8**	**$172.2**	**$322.8**	**$452.8**	**$146.9**	**$191.5**
		81%	**86%**	**90%**	**81%**	**81%**	**62%**	**94%**	**89%**	**90%**	**81%**	**95%**	**97%**	**89%**	**85%**
	Total (with Phase 4 costs)	**$139.1**	**$202.7**	**$165.7**	**$179.4**	**$232.7**	**$254.0**	**$103.3**	**$237.7**	**$123.9**	**$213.7**	**$338.6**	**$467.6**	**$165.0**	**$226.3**
		100%	**100%**	**100%**	**100%**	**100%**	**100%**	**100%**	**100%**	**100%**	**100%**	**100%**	**100%**	**100%**	**100%**
Expected	Non-clinical	$136.1	$363.6	$359.8	$268.5	$292.5	$360.5	$143.0	$284.2	$496.6	$268.4	$491.8	$764.1	$227.6	$353.5
		36%	41%	40%	39%	38%	37%	36%	39%	41%	39%	41%	44%	38%	40%
	Clinical Phases	$191.6	$472.1	$492.2	$355.8	$416.8	$480.5	$220.2	$384.1	$676.0	$350.8	$659.0	$950.0	$334.7	$465.7

Parameter	Phase	Anti-Infective	Cardiovascular	Central Nervous System	Dermatology	Endocrine	Gastrointestinal	Genitourinary System	Hematology	Oncology	Respiratory System	Ophthalmology	Pain and Anesthesia	Immunomodulation	All Therapeutic Areas
		51%	53%	55%	52%	53%	50%	56%	53%	56%	51%	55%	54%	55%	53%
	Phase 1	$21.3	$82.3	$151.5	$97.8	$77.1	$70.1	$43.4	$144.9	$290.8	$51.5	$63.4	$109.5	$73.7	$110.6
		6%	9%	17%	14%	10%	7%	11%	20%	24%	8%	5%	6%	12%	13%
	Phase 2	$98.0	$120.2	$180.2	$112.1	$130.4	$256.7	$112.7	$113.2	$259.7	$127.6	$142.2	$310.7	$156.3	$163.4
		26%	14%	20%	16%	17%	27%	29%	16%	21%	19%	12%	18%	26%	19%
	Phase 3	$72.2	$269.7	$160.5	$145.9	$209.3	$153.8	$64.0	$126.0	$125.4	$171.6	$453.4	$529.8	$104.6	$191.6
		19%	30%	18%	21%	27%	16%	16%	17%	10%	25%	38%	30%	17%	22%
	FDA Submission	$25.2	$25.8	$26.0	$24.9	$25.7	$25.6	$25.7	$25.3	$24.6	$25.7	$24.9	$27.3	$25.5	$25.4
		7%	3%	3%	4%	3%	3%	6%	4%	2%	4%	2%	2%	4%	3%
	Post-approval Phase	$25.8	$28.9	$16.6	$33.9	$45.0	$96.9	$6.0	$26.7	$12.1	$41.5	$15.9	$14.8	$18.1	$34.7
		7%	3%	2%	5%	6%	10%	2%	4%	1%	6%	1%	1%	3%	4%
	Total (without Phase 4 costs)	**$352.9**	**$861.5**	**$878.0**	**$649.3**	**$735.0**	**$866.6**	**$388.9**	**$693.6**	**$1,197.2**	**$644.9**	**$1,175.8**	**$1,741.5**	**$587.7**	**$844.6**
		93%	**97%**	**98%**	**95%**	**94%**	**90%**	**98%**	**96%**	**99%**	**94%**	**99%**	**99%**	**97%**	**96%**
	Total (with Phase 4 costs)	**$378.7**	**$890.3**	**$894.6**	**$683.1**	**$780.0**	**$963.5**	**$394.9**	**$720.4**	**$1,209.2**	**$686.4**	**$1,191.6**	**$1,756.2**	**$605.8**	**$879.3**
		100%	**100%**	**100%**	**100%**	**100%**	**100%**	**100%**	**100%**	**100%**	**100%**	**100%**	**100%**	**100%**	**100%**

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 cost of capital.

[d] The figures represent the out-of-pocket costs at the point of launch after adjusting for the cost of capital; computed in accordance with approach described in Section 3. Capitalized out-of-pocket costs take into account the cost of capital but not the costs of failures.

[e] Expected capitalized costs take into account the costs of failures and the cost of capital.

As indicated, expected capitalized costs are higher than out-of-pocket costs because they consider the opportunity cost of capital that embodies the time value of money and the fact that there will be failures along the way. The figures presented in Table 10 represent our baseline cost of new drug development against which we evaluate different strategies designed to improve likelihood of phase transition success and/or reduce non-clinical, clinical, FDA NDA/BLA phase, and post-approval related costs and durations.

As Table 10 illustrates, the primary driver of development cost is clinical stage followed by non-clinical stage expenditures when we account for cost of failures and 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 and clinical development stages account for 13 percent and 70 percent of total capitalized development costs, respectively, whether or not post-approval Phase 4 study 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 40 percent, inclusive of post-approval study costs. Non-clinical stage represents the second largest portion of total expected capitalized development costs following the clinical stage at 53 percent primarily because the probability of moving from non-clinical stage to a marketable drug is only 8.5 percent on average. Thus, the $11.8 million and nearly 3 years needed to conduct non-clinical studies are much greater in real economic impact than their nominal value suggests. As the drug developer successfully transitions from one development stage to another, the likelihood of approval hence expected returns change. Even though a large, Phase 3 study may be more expensive out-of-pocket than non-clinical work, the odds of a drug candidate making it to market is significantly higher (65.5 percent) if the new drug candidate has already cleared the non-clinical, Phase 1, and Phase 2 stages than one that is at the target identification stage (8.5 percent).

The clinical phases of drug development (Phase 1, 2, and 3) are the largest contributor to total out of pocket development costs, comprising around 68 percent of total costs inclusive of post-approval studies. From a capitalized out-of-pocket cost perspective, clinical development comprises 70 percent of total capitalized development costs, including post-approval costs but excluding 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 53 percent, including post-approval study costs. Phase 3 costs constitute the vast majority of clinical development costs, due primarily to enrolling large number of patients (approximately 630 versus 51 for Phase 1), taking longer than Phase 1 (38.0 months versus 27.8 months), and greater out-of-pocket costs (approximately $89.3 million vs. $7.1 million).

It is important to note that the estimated costs presented in this study do not include some significant elements, such as development of chemistry, manufacturing, and controls (CMC), and manufacturing plant design and build, which could be significant.

5.11 IMPACT OF SELECT CLINICAL TRIAL STRATEGIES ON THE TOTAL COST OF DRUG DEVELOPMENT

As described in our previous study (Eastern Research Group, Inc., 2022), we asked our panel of experts to evaluate the impact of various clinical study strategies on the cost, duration, and phase transition success probability of drug development stages. A summary of our experts' estimates is presented in Table 12 and estimates by therapeutic area are provided in Appendix A. Negative percentages indicate reductions in a given parameter (e.g., use of mobile technologies would *reduce* clinical study costs, on average, by 3 percent during Phase 1 holding all other factors constant), and positive percentages indicate increases in a given parameter (e.g., using biomarkers as surrogate endpoints would *increase* a developer's probability of successfully transitioning from Phase 2 to Phase 3, on average, by 2 percent across all therapeutic areas holding all other factors constant).

We then evaluated the overall impact of each strategy on total expected development cost (see Table 13). Using our total expected capitalized cost (including post-approval studies) estimates as our baseline, we evaluated the change (or delta [Δ]) to this total expected cost if a developer were to implement a given strategy across all therapeutic areas. For each strategy, we evaluated the reduction in overall expected development cost attributable to the cost savings, time savings, and increases in phase transition success probability associated with that strategy. For example, use of adaptive design in clinical trial protocols are associated with sponsor overall cost savings of 22.8 percent, time savings of 1.6 percent, and a phase transition success probability increase of 19.2 percent (Table 13). When incorporated into our drug development cost model, these changes result in a total expected capitalized development cost of $678.7 million, which is 22.8 percent lower than our baseline estimate of $879.3 million.

From Table 13, the strategy with the largest impact on overall development costs across all therapeutic areas is Improvements in FDA Review Process Efficiency and Interactions (-27.1 percent), followed by Adaptive Design (-22.8 percent), and implementation of a Simplified Clinical Trial Protocols and Reduced Amendments (-22.2 percent). Those strategies with the lowest expected development cost savings across all therapeutic areas include Use of Patient Registries (-9.9 percent), Biomarkers as Surrogate Endpoints (-13.3 percent), and Electronic Health Records (-13.6 percent).

Table 12. Expert Estimates of Strategy Impacts on Cost, Duration, and Probability of Phase Transition Success for Drugs (All Therapeutic Areas Combined)

Strategy	Phase	Cost	Duration	Success Likelihood
Mobile Technologies	Non-clinical	-1%	0%	0%
	Phase 1	-3%	-3%	2%
	Phase 2	-8%	-6%	4%
	Phase 3	-15%	-9%	5%
	FDA Review	-6%	-1%	1%
	Phase 4	-21%	-9%	NA
Simplified Clinical Trial Protocols and Reduced Amendments	Non-clinical	-4%	-3%	0%
	Phase 1	-5%	-5%	1%
	Phase 2	-9%	-8%	4%
	Phase 3	-13%	-9%	6%
	FDA Review	-3%	-3%	1%
	Phase 4	-10%	-7%	NA
Reduced SDV	Non-clinical	-1%	0%	0%
	Phase 1	-5%	-2%	0%
	Phase 2	-10%	-5%	0%
	Phase 3	-18%	-10%	0%
	FDA Review	-12%	-7%	0%
	Phase 4	-17%	-7%	NA
Improvements in FDA Review Efficiency and Interactions	Non-clinical	-1%	0%	4%
	Phase 1	-2%	-2%	2%
	Phase 2	-4%	-3%	10%
	Phase 3	-10%	-8%	13%
	FDA Review	-2%	-1%	6%
	Phase 4	-5%	-3%	NA
Staged Approval	Non-clinical	0%	0%	0%
	Phase 1	0%	0%	2%
	Phase 2	-2%	-2%	7%
	Phase 3	-12%	-9%	6%
	FDA Review	-5%	-5%	4%
	Phase 4	-1%	-1%	NA
Biomarkers as Surrogate Endpoints	Non-clinical	-4%	-2%	5%
	Phase 1	-3%	-2%	6%
	Phase 2	-1%	-3%	2%

Strategy	Phase	Cost	Duration	Success Likelihood
	Phase 3	-5%	-3%	4%
	FDA Review	-3%	-3%	2%
	Phase 4	-3%	-2%	NA
Electronic Health Records	Non-clinical	-1%	-1%	0%
	Phase 1	0%	-3%	2%
	Phase 2	-5%	-4%	2%
	Phase 3	-8%	-8%	3%
	Phase 3L	-9%	-9%	3%
	Phase 3N	-8%	-8%	3%
	FDA Review	-5%	-7%	1%
	Phase 4	-15%	-13%	NA
Patient Registries	Non-clinical	0%	0%	0%
	Phase 1	-5%	-5%	0%
	Phase 2	-5%	-5%	0%
	Phase 3	-6%	-6%	1%
	Phase 3L	-8%	-8%	2%
	Phase 3N	-6%	-6%	1%
	FDA Review	-4%	-5%	0%
	Phase 4	-7%	-8%	NA
Adaptive Design	Non-clinical	0%	0%	0%
	Phase 1	6%	7%	4%
	Phase 2	-1%	1%	14%
	Phase 3	-8%	-9%	10%
	FDA Review	-1%	-2%	6%
	Phase 4	-3%	-3%	NA
Standardized Contracts	Non-clinical	-4%	-5%	0%
	Phase 1	-6%	-7%	0%
	Phase 2	-7%	-9%	0%
	Phase 3	-9%	-12%	0%
	FDA Review	-3%	-5%	0%
	Phase 4	-8%	-9%	NA

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.[

Table 13. Impacts of Clinical Trial Strategies on Baseline Cost, Duration, and Phase Transition Success Probability – Drugs

Strategy	Therapeutic Area (TA)	Change from Baseline due to…							
		Change in Cost		Change in Duration		Change in Success Probability		Total Change [a]	
		$	%	$	%	$	%	$	%
Mobile Technologies	Anti-Infective	-$35.9	-9.5%	-$10.6	-2.8%	-$22.4	-5.9%	-$63.8	-16.9%
	Cardiovascular	-$103.3	-11.6%	-$37.6	-4.2%	-$70.9	-8.0%	-$193.6	-21.7%
	Central Nervous System	-$85.1	-9.5%	-$45.4	-5.1%	-$70.9	-7.9%	-$183.3	-20.5%
	Dermatology	-$71.6	-10.5%	-$27.8	-4.1%	-$49.8	-7.3%	-$136.5	-20.0%
	Endocrine	-$92.0	-11.8%	-$29.9	-3.8%	-$71.0	-9.1%	-$176.2	-22.6%
	Gastrointestinal	-$107.2	-11.1%	-$37.4	-3.9%	-$68.7	-7.1%	-$195.8	-20.3%
	Genitourinary System	-$37.6	-9.5%	-$13.8	-3.5%	-$30.4	-7.7%	-$74.9	-19.0%
	Hematology	-$67.5	-9.4%	-$40.2	-5.6%	-$56.0	-7.8%	-$149.1	-20.7%
	Oncology	-$83.0	-6.9%	-$69.0	-5.7%	-$105.3	-8.7%	-$235.3	-19.5%
	Respiratory System	-$83.5	-12.2%	-$30.0	-4.4%	-$40.1	-5.8%	-$141.2	-20.6%
	Ophthalmology	-$151.2	-12.7%	-$39.7	-3.3%	-$77.5	-6.5%	-$245.6	-20.6%
	Pain and Anesthesia	-$216.3	-12.3%	-$73.8	-4.2%	-$114.8	-6.5%	-$369.5	-21.0%
	Immunomodulation	-$55.1	-9.1%	-$22.3	-3.7%	-$43.2	-7.1%	-$110.9	-18.3%
	All Therapeutic Areas	**-$93.1**	**-10.6%**	**-$36.7**	**-4.2%**	**-$64.9**	**-7.4%**	**-$178.0**	**-20.2%**
Simplified Clinical Trial Protocols and Reduced Amendments	Anti-Infective	-$38.0	-10.0%	-$16.2	-4.3%	-$28.6	-7.6%	-$70.4	-18.6%
	Cardiovascular	-$130.1	-14.6%	-$58.3	-6.5%	-$112.1	-12.6%	-$254.8	-28.6%
	Central Nervous System	-$94.6	-10.6%	-$63.0	-7.0%	-$88.2	-9.9%	-$205.1	-22.9%
	Dermatology	-$74.4	-10.9%	-$40.4	-5.9%	-$63.0	-9.2%	-$148.6	-21.8%
	Endocrine	-$98.8	-12.7%	-$42.7	-5.5%	-$63.8	-8.2%	-$174.1	-22.3%
	Gastrointestinal	-$106.3	-11.0%	-$55.0	-5.7%	-$86.8	-9.0%	-$208.1	-21.6%
	Genitourinary System	-$41.1	-10.4%	-$20.2	-5.1%	-$37.7	-9.5%	-$83.2	-21.1%
	Hematology	-$74.2	-10.3%	-$54.5	-7.6%	-$69.4	-9.6%	-$165.4	-23.0%
	Oncology	-$109.4	-9.0%	-$102.0	-8.4%	-$121.4	-10.0%	-$282.3	-23.3%
	Respiratory System	-$82.4	-12.0%	-$36.5	-5.3%	-$52.3	-7.6%	-$145.2	-21.2%
	Ophthalmology	-$150.7	-12.7%	-$60.0	-5.0%	-$104.5	-8.8%	-$263.3	-22.1%
	Pain and Anesthesia	-$238.7	-13.6%	-$110.4	-6.3%	-$151.9	-8.7%	-$420.0	-23.9%
	Immunomodulation	-$63.1	-10.4%	-$32.4	-5.3%	-$53.9	-8.9%	-$126.2	-20.8%
	All Therapeutic Areas	**-$97.7**	**-11.1%**	**-$53.7**	**-6.1%**	**-$82.5**	**-9.4%**	**-$195.1**	**-22.2%**
Reduced SDV	Anti-Infective	-$42.1	-11.1%	-$12.9	-3.4%	-$2.9	-0.8%	-$54.6	-14.4%
	Cardiovascular	-$141.0	-15.8%	-$67.0	-7.5%	$57.9	6.5%	-$127.5	-14.3%
	Central Nervous System	-$105.2	-11.8%	-$54.0	-6.0%	-$9.7	-1.1%	-$156.4	-17.5%
	Dermatology	-$86.5	-12.7%	-$33.5	-4.9%	-$6.9	-1.0%	-$118.0	-17.3%

Strategy	Therapeutic Area (TA)	Change from Baseline due to…							
		Change in Cost		Change in Duration		Change in Success Probability		Total Change [a]	
		$	%	$	%	$	%	$	%
	Endocrine	-$98.4	-12.6%	-$31.7	-4.1%	-$6.7	-0.9%	-$128.3	-16.4%
	Gastrointestinal	-$121.8	-12.6%	-$45.2	-4.7%	-$9.2	-1.0%	-$164.5	-17.1%
	Genitourinary System	-$46.2	-11.7%	-$17.3	-4.4%	-$4.0	-1.0%	-$63.0	-16.0%
	Hematology	-$83.9	-11.6%	-$48.7	-6.8%	-$7.8	-1.1%	-$129.8	-18.0%
	Oncology	-$102.2	-8.4%	-$75.1	-6.2%	-$11.7	-1.0%	-$175.5	-14.5%
	Respiratory System	-$85.1	-12.4%	-$31.9	-4.6%	-$5.4	-0.8%	-$114.7	-16.7%
	Ophthalmology	-$183.0	-15.4%	-$46.8	-3.9%	-$10.6	-0.9%	-$225.0	-18.9%
	Pain and Anesthesia	-$232.5	-13.2%	-$95.5	-5.4%	-$15.7	-0.9%	-$319.2	-18.2%
	Immunomodulation	-$66.7	-11.0%	-$26.8	-4.4%	-$5.7	-0.9%	-$92.7	-15.3%
	All Therapeutic Areas	**-$112.3**	**-12.8%**	**-$43.3**	**-4.9%**	**-$8.9**	**-1.0%**	**-$153.1**	**-17.4%**
Improvements in FDA Review Efficiency and Interactions	Anti-Infective	-$22.4	-5.9%	-$10.3	-2.7%	-$66.3	-17.5%	-$91.1	-24.1%
	Cardiovascular	-$80.8	-9.1%	-$37.3	-4.2%	-$170.5	-19.1%	-$260.3	-29.2%
	Central Nervous System	-$50.3	-5.6%	-$35.7	-4.0%	-$190.2	-21.3%	-$252.5	-28.2%
	Dermatology	-$41.4	-6.1%	-$22.1	-3.2%	-$135.1	-19.8%	-$181.9	-26.6%
	Endocrine	-$66.2	-8.5%	-$26.6	-3.4%	-$138.2	-17.7%	-$209.9	-26.9%
	Gastrointestinal	-$55.3	-5.7%	-$30.4	-3.2%	-$186.9	-19.4%	-$250.0	-25.9%
	Genitourinary System	-$21.0	-5.3%	-$11.2	-2.8%	-$82.0	-20.8%	-$105.3	-26.7%
	Hematology	-$40.1	-5.6%	-$33.0	-4.6%	-$149.4	-20.7%	-$202.6	-28.1%
	Oncology	-$50.6	-4.2%	-$64.2	-5.3%	-$243.4	-20.1%	-$328.7	-27.2%
	Respiratory System	-$42.8	-6.2%	-$22.8	-3.3%	-$125.0	-18.2%	-$174.6	-25.4%
	Ophthalmology	-$94.3	-7.9%	-$32.4	-2.7%	-$222.4	-18.7%	-$318.0	-26.7%
	Pain and Anesthesia	-$117.8	-6.7%	-$57.6	-3.3%	-$325.1	-18.5%	-$457.5	-26.0%
	Immunomodulation	-$31.4	-5.2%	-$18.2	-3.0%	-$118.4	-19.5%	-$155.1	-25.6%
	All Therapeutic Areas	**-$54.2**	**-6.2%**	**-$29.3**	**-3.3%**	**-$176.9**	**-20.1%**	**-$238.2**	**-27.1%**
Staged Approval	Anti-Infective	-$17.3	-4.6%	-$8.8	-2.3%	-$40.0	-10.6%	-$63.2	-16.7%
	Cardiovascular	-$53.1	-6.0%	-$25.9	-2.9%	-$80.7	-9.1%	-$151.7	-17.0%
	Central Nervous System	-$44.2	-4.9%	-$37.2	-4.2%	-$114.8	-12.8%	-$185.4	-20.7%
	Dermatology	-$38.5	-5.6%	-$22.1	-3.2%	-$80.8	-11.8%	-$133.8	-19.6%
	Endocrine	-$47.0	-6.0%	-$22.0	-2.8%	-$81.3	-10.4%	-$142.5	-18.3%
	Gastrointestinal	-$45.0	-4.7%	-$30.9	-3.2%	-$112.5	-11.7%	-$178.5	-18.5%
	Genitourinary System	-$18.2	-4.6%	-$12.0	-3.0%	-$49.6	-12.6%	-$76.0	-19.2%
	Hematology	-$35.3	-4.9%	-$35.1	-4.9%	-$90.3	-12.5%	-$151.2	-21.0%
	Oncology	-$37.9	-3.1%	-$68.5	-5.7%	-$182.3	-15.1%	-$271.9	-22.5%

Strategy	Therapeutic Area (TA)	Change from Baseline due to…							
		Change in Cost		Change in Duration		Change in Success Probability		Total Change [a]	
		$	%	$	%	$	%	$	%
	Respiratory System	-$43.8	-6.4%	-$25.5	-3.7%	-$81.1	-11.8%	-$140.9	-20.5%
	Ophthalmology	-$104.3	-8.8%	-$31.5	-2.6%	-$128.2	-10.8%	-$248.2	-20.8%
	Pain and Anesthesia	-$122.6	-7.0%	-$64.5	-3.7%	-$189.3	-10.8%	-$354.3	-20.2%
	Immunomodulation	-$26.7	-4.4%	-$18.4	-3.0%	-$70.7	-11.7%	-$110.4	-18.2%
	All Therapeutic Areas	**-$50.6**	**-5.7%**	**-$29.0**	**-3.3%**	**-$105.7**	**-12.0%**	**-$175.1**	**-19.9%**
Biomarkers as Surrogate Endpoints	Anti-Infective	-$27.5	-7.3%	-$16.4	-4.3%	-$30.4	-8.0%	-$58.9	-15.6%
	Cardiovascular	-$38.6	-4.3%	-$26.5	-3.0%	-$58.5	-6.6%	-$96.7	-10.9%
	Central Nervous System	-$42.8	-4.8%	-$36.1	-4.0%	-$81.8	-9.1%	-$126.4	-14.1%
	Dermatology	-$33.8	-4.9%	-$24.7	-3.6%	-$58.4	-8.6%	-$91.5	-13.4%
	Endocrine	-$36.0	-4.6%	-$23.4	-3.0%	-$57.6	-7.4%	-$91.9	-11.8%
	Gastrointestinal	-$41.5	-4.3%	-$32.9	-3.4%	-$75.0	-7.8%	-$115.9	-12.0%
	Genitourinary System	-$16.8	-4.2%	-$12.6	-3.2%	-$33.1	-8.4%	-$49.1	-12.4%
	Hematology	-$35.3	-4.9%	-$31.2	-4.3%	-$66.3	-9.2%	-$105.1	-14.6%
	Oncology	-$42.2	-3.5%	-$51.5	-4.3%	-$124.4	-10.3%	-$181.7	-15.0%
	Respiratory System	-$29.3	-4.3%	-$21.2	-3.1%	-$46.3	-6.7%	-$75.5	-11.0%
	Ophthalmology	-$67.8	-5.7%	-$38.5	-3.2%	-$93.5	-7.9%	-$154.2	-12.9%
	Pain and Anesthesia	-$87.5	-5.0%	-$66.6	-3.8%	-$134.5	-7.7%	-$222.9	-12.7%
	Immunomodulation	-$30.0	-5.0%	-$23.5	-3.9%	-$52.8	-8.7%	-$81.0	-13.4%
	All Therapeutic Areas	**-$43.3**	**-4.9%**	**-$31.9**	**-3.6%**	**-$75.3**	**-8.6%**	**-$117.3**	**-13.3%**
Electronic Health Records	Anti-Infective	-$26.0	-6.9%	-$12.3	-3.2%	-$13.2	-3.5%	-$47.8	-12.6%
	Cardiovascular	-$62.8	-7.1%	-$40.1	-4.5%	-$30.0	-3.4%	-$123.0	-13.8%
	Central Nervous System	-$46.3	-5.2%	-$47.6	-5.3%	-$42.8	-4.8%	-$125.3	-14.0%
	Dermatology	-$40.2	-5.9%	-$30.7	-4.5%	-$30.3	-4.4%	-$92.8	-13.6%
	Endocrine	-$63.2	-8.1%	-$34.0	-4.4%	-$30.1	-3.9%	-$117.7	-15.1%
	Gastrointestinal	-$62.6	-6.5%	-$39.6	-4.1%	-$40.6	-4.2%	-$131.7	-13.7%
	Genitourinary System	-$21.0	-5.3%	-$15.4	-3.9%	-$17.9	-4.5%	-$49.9	-12.7%
	Hematology	-$36.6	-5.1%	-$43.3	-6.0%	-$34.1	-4.7%	-$104.6	-14.5%
	Oncology	-$39.0	-3.2%	-$77.0	-6.4%	-$51.4	-4.2%	-$154.6	-12.8%
	Respiratory System	-$40.1	-5.8%	-$28.0	-4.1%	-$24.2	-3.5%	-$85.3	-12.4%
	Ophthalmology	-$86.2	-7.2%	-$41.9	-3.5%	-$48.1	-4.0%	-$161.4	-13.5%
	Pain and Anesthesia	-$108.9	-6.2%	-$87.4	-5.0%	-$69.9	-4.0%	-$243.6	-13.9%
	Immunomodulation	-$30.8	-5.1%	-$23.4	-3.9%	-$25.7	-4.2%	-$73.6	-12.2%
	All Therapeutic Areas	**-$52.3**	**-5.9%**	**-$38.5**	**-4.4%**	**-$39.3**	**-4.5%**	**-$119.4**	**-13.6%**

Strategy	Therapeutic Area (TA)	Change from Baseline due to…							
		Change in Cost		Change in Duration		Change in Success Probability		Total Change [a]	
		$	%	$	%	$	%	$	%
Patient Registries	Anti-Infective	-$17.9	-4.7%	-$9.2	-2.4%	-$3.0	-0.8%	-$29.5	-7.8%
	Cardiovascular	-$41.6	-4.7%	-$26.3	-3.0%	-$6.6	-0.7%	-$72.8	-8.2%
	Central Nervous System	-$48.9	-5.5%	-$39.5	-4.4%	-$9.3	-1.0%	-$94.6	-10.6%
	Dermatology	-$38.0	-5.6%	-$25.6	-3.7%	-$6.6	-1.0%	-$68.2	-10.0%
	Endocrine	-$42.7	-5.5%	-$21.8	-2.8%	-$6.7	-0.9%	-$69.6	-8.9%
	Gastrointestinal	-$53.8	-5.6%	-$33.3	-3.5%	-$9.2	-1.0%	-$93.7	-9.7%
	Genitourinary System	-$21.2	-5.4%	-$12.0	-3.0%	-$4.0	-1.0%	-$36.3	-9.2%
	Hematology	-$39.5	-5.5%	-$35.7	-5.0%	-$7.2	-1.0%	-$79.8	-11.1%
	Oncology	-$51.6	-4.3%	-$54.3	-4.5%	-$10.8	-0.9%	-$113.5	-9.4%
	Respiratory System	-$34.3	-5.0%	-$24.4	-3.6%	-$5.4	-0.8%	-$62.4	-9.1%
	Ophthalmology	-$68.4	-5.7%	-$33.3	-2.8%	-$10.9	-0.9%	-$109.8	-9.2%
	Pain and Anesthesia	-$91.6	-5.2%	-$69.9	-4.0%	-$15.8	-0.9%	-$172.2	-9.8%
	Immunomodulation	-$30.4	-5.0%	-$18.9	-3.1%	-$5.7	-0.9%	-$53.7	-8.9%
	All Therapeutic Areas	**-$48.9**	**-5.6%**	**-$32.5**	**-3.7%**	**-$8.6**	**-1.0%**	**-$87.4**	**-9.9%**
Adaptive Design	Anti-Infective	-$12.3	-3.2%	-$5.8	-1.5%	-$61.0	-16.1%	-$76.3	-20.1%
	Cardiovascular	-$34.0	-3.8%	-$15.9	-1.8%	-$129.1	-14.5%	-$172.6	-19.4%
	Central Nervous System	-$14.9	-1.7%	-$21.6	-2.4%	-$184.9	-20.7%	-$215.8	-24.1%
	Dermatology	-$16.4	-2.4%	-$9.8	-1.4%	-$129.5	-19.0%	-$152.3	-22.3%
	Endocrine	-$29.9	-3.8%	-$13.3	-1.7%	-$129.9	-16.6%	-$166.9	-21.4%
	Gastrointestinal	-$24.7	-2.6%	-$15.1	-1.6%	-$180.2	-18.7%	-$213.6	-22.2%
	Genitourinary System	-$7.5	-1.9%	-$7.4	-1.9%	-$79.9	-20.2%	-$92.4	-23.4%
	Hematology	-$9.8	-1.4%	-$21.3	-3.0%	-$145.8	-20.2%	-$172.2	-23.9%
	Oncology	-$17.2	-1.4%	-$48.1	-4.0%	-$258.5	-21.4%	-$311.4	-25.8%
	Respiratory System	-$24.5	-3.6%	-$13.9	-2.0%	-$108.6	-15.8%	-$141.2	-20.6%
	Ophthalmology	-$62.3	-5.2%	-$17.8	-1.5%	-$200.7	-16.8%	-$268.7	-22.5%
	Pain and Anesthesia	-$70.7	-4.0%	-$30.9	-1.8%	-$300.4	-17.1%	-$386.8	-22.0%
	Immunomodulation	-$15.4	-2.5%	-$13.7	-2.3%	-$116.5	-19.2%	-$140.8	-23.2%
	All Therapeutic Areas	**-$23.1**	**-2.6%**	**-$13.7**	**-1.6%**	**-$169.1**	**-19.2%**	**-$200.6**	**-22.8%**
Standardized Contracts	Anti-Infective	-$28.4	-7.5%	-$20.7	-5.5%	-$6.7	-1.8%	-$44.9	-11.8%
	Cardiovascular	-$97.6	-11.0%	-$76.3	-8.6%	-$50.0	-5.6%	-$175.4	-19.7%
	Central Nervous System	-$77.6	-8.7%	-$77.6	-8.7%	-$20.7	-2.3%	-$140.6	-15.7%
	Dermatology	-$59.9	-8.8%	-$49.7	-7.3%	-$15.1	-2.2%	-$99.1	-14.5%
	Endocrine	-$71.9	-9.2%	-$50.4	-6.5%	-$15.2	-1.9%	-$111.4	-14.3%

Strategy	Therapeutic Area (TA)	Change from Baseline due to…							
		Change in Cost		Change in Duration		Change in Success Probability		Total Change [a]	
		$	%	$	%	$	%	$	%
	Gastrointestinal	-$83.8	-8.7%	-$68.1	-7.1%	-$20.7	-2.1%	-$138.0	-14.3%
	Genitourinary System	-$33.1	-8.4%	-$25.3	-6.4%	-$8.5	-2.1%	-$53.2	-13.5%
	Hematology	-$61.8	-8.6%	-$67.0	-9.3%	-$16.3	-2.3%	-$116.9	-16.2%
	Oncology	-$83.6	-6.9%	-$113.6	-9.4%	-$23.4	-1.9%	-$181.1	-15.0%
	Respiratory System	-$53.0	-7.7%	-$52.1	-7.6%	-$12.8	-1.9%	-$95.6	-13.9%
	Ophthalmology	-$113.5	-9.5%	-$74.5	-6.2%	-$26.5	-2.2%	-$168.5	-14.1%
	Pain and Anesthesia	-$152.8	-8.7%	-$136.5	-7.8%	-$38.5	-2.2%	-$260.2	-14.8%
	Immunomodulation	-$47.8	-7.9%	-$39.5	-6.5%	-$12.3	-2.0%	-$79.7	-13.2%
	All Therapeutic Areas	**-$78.0**	**-8.9%**	**-$66.3**	**-7.5%**	**-$19.9**	**-2.3%**	**-$130.3**	**-14.8%**

[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.

6 DISCUSSION

It is difficult to directly compare cost of drug development estimates across different studies. As shown in multiple studies, expected capitalized cost of drug development estimates are highly sensitive to cost of capital and phase transition success probability assumptions. Our study uses a cost of capital of 11 percent whereas others use cost of capital figures ranging from 0 percent, 7 percent, and 10.5 percent.

Even small deviations in the cost of capital can result in significant swings in expected capitalized costs. For example, when the cost of capital is 11 percent, the expected capitalized cost (excluding post-approval study costs) for oncology drugs is $1,209.2 million (Table 11). If the cost of capital is reduced by half a percentage point to 10.5 percent, the estimated expected capitalized cost figure decreases to $1,170.6 million (a reduction of $38.6 million).

There also are differences in how therapeutic areas are defined across studies. For example, Wouters, et al (2020) group antineoplastic (i.e., anticancer) and immunomodulating agents together whereas this study considers them to be two distinct therapeutic areas (i.e., oncology and immunomodulation). Similarly, they group alimentary tract and metabolism drugs together whereas this study separates them into gastrointestinal and endocrine therapeutic areas. Finally, this study includes costs for FDA review (around $2.6 million) whereas the other studies do not incorporate these costs.

The projected estimates of overall cost savings from different strategies likely have large uncertainty bounds. First, these estimates reflect opinions of a relatively small group of experts; they are not based on controlled experiments (e.g., comparing the cost, duration, phase transition success probability of a sufficiently large sample of trials that use adaptive designs to those that do not). Numerous studies have shown that expert opinion could be biased and subject to high degree of variability. Second, the onerous nature of the expert elicitation did not allow for in-depth follow-up discussions to gain a better understanding of the mental models experts were using when thinking about the different strategies. For example, each expert might have had a different set of FDA guidance documents that could benefit from further clarity and/or consistency when evaluating the expected impact of FDA Review Process Efficiency and Interactions strategy. Additionally, experts did not account for the additional resource burden associated with implementation of such strategies nor policies that may already be in place but are not necessarily public knowledge (e.g., internal training programs for FDA reviewers, planned or ongoing updates to FDA guidances).

7 CONCLUSIONS

Similar to other published studies (DiMasi, et al., 2016; Wouters, et al., 2020; Prasad & Mailankody, 2017; Makower, et al., 2010; Chit, et al., 2014; Gouglas, et al., 2018), we find that clinical trials comprise the largest portion of overall drug development costs (Table 11). Clinical phase costs account for around 68 percent of out-of-pocket R&D expenditures for drugs. While our finding on the relative contribution of clinical trial costs to overall R&D expenditures is in

line with other published studies, the estimated magnitude of these costs is different. We find that the clinical phase costs around $117.4 million out-of-pocket on average (ranging from $55.3 for genitourinary system to $255.1 million for pain and anesthesia drugs) in 2018 dollars compared to $386.8 million[9] reported by DiMasi et al. (2016) and $319.3 million (ranging from $73.8 million to $2,119.9 million) reported by Wouters et al. (2020).

Despite the disproportionately high contribution of non-clinical phase costs to overall expected capitalized development costs, there is very little data on non-clinical phase costs. A 2012 study by Tufts CSDD estimated the non-clinical costs supporting a drug development program at $7.2 million, ranging from around $815,000 to $23.4 million with chemistry and manufacturing control activity costs representing the largest share at approximately 50 percent, followed by toxicology studies comprising nearly 25 percent, and pharmacology studies comprising 10 percent of the total non-clinical budget (Stergiopoulos, et al., 2013).[10] This earlier estimate of non-clinical costs is substantially lower than the updated estimate in DiMasi et al., (2016), where the figure is extrapolated using the ratio of total pre-human development costs to total R&D spending, 42.9 percent; the approach generally adopted in this study.[11] Given the sizable contribution of non-clinical phase costs to overall expected capitalized costs, further research into this stage is needed.

Using the information from experts and other relevant data on drug development costs, we estimate how implementation of the strategies impact drug development costs (Figure 2).

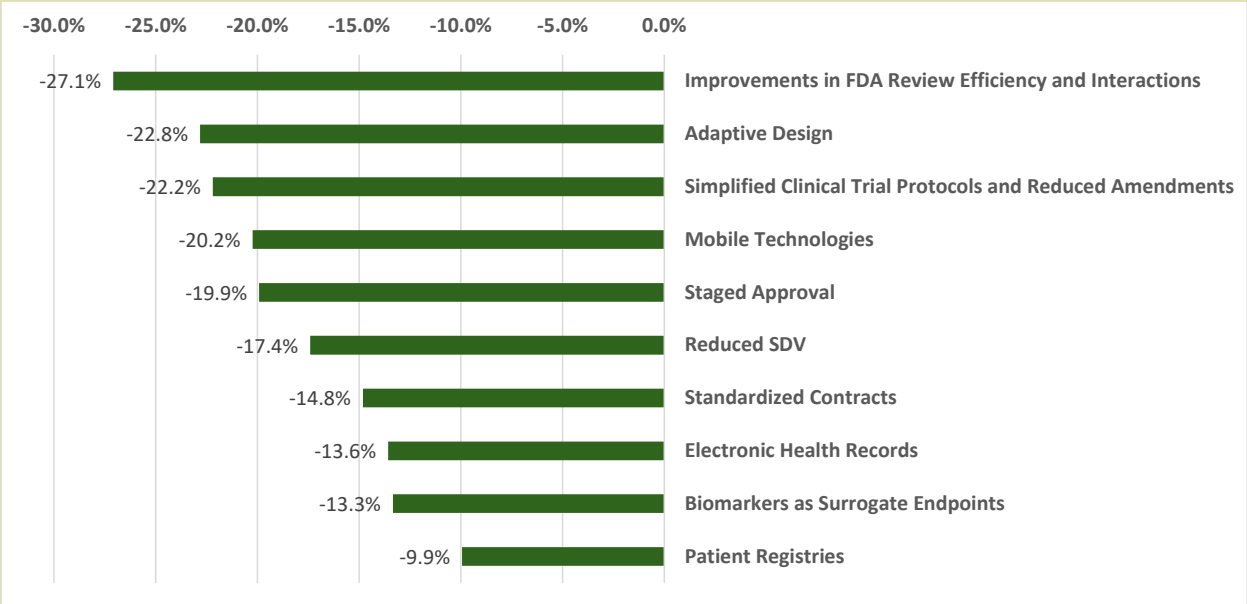
Improving FDA review process efficiency and interactions has the largest projected impact (-27.1 percent) on overall development costs across all therapeutic areas. This is followed by adaptive design (-22.8 percent), and implementation of simplified clinical trial protocols and reduced amendments (-22.2 percent). Strategies with the lowest, but still sizeable, expected development cost savings include the use of patient registries (-9.9 percent), biomarkers as surrogate endpoint (-13.3 percent), electronic health records (-13.6 percent), and use of standardized contracts (-14.8 percent).

[9] The corresponding value reported in DiMasi et al. (2016) is $339.3 million in 2013 dollars.

[10] The corresponding values reported in Stergiopoulos, et al. (2013) are $6.2 million, $698,000, and $20 million in 2012 dollars.

[11] Since we had estimates of average non-clinical duration and transition success probability, we used the preclinical spending ($430 million) and clinical costs ($965 million) per approved drug reported in Figure 2 of DiMasi et al (2016) ,which translates to a ratio of 44.6 percent—1.7 percentage points higher than the 42.9 percent figure used in other studies.

Figure 2. Estimated Impacts on Expected Capitalized Development Costs (Inclusive of Post-approval Costs) for Drugs 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.

8 REFERENCES

Abrantes-Metz, R. M., Adams, C. P. & Metz, A., 2004. *Pharmaceutical Development Phases: A Duration Analysis - Working Paper 274,* Washington, DC: Federal Trade Commission, Bureau of Economics.

Adams, C. & Brantner, V., 2006. Estimating the cost of new drug development: is it really 802 million dollars?. *Health Affairs (Millwood),* 25(2), pp. 420-428.

Adams, C. & Brantner, V., 2010. Spending on new drug development. *Health Economics,* 19(2), pp. 130-141.

BiomedTracker, 2016. *Clinical Development Success Rates 2006-2015,* Washington, DC: Biotechnology Innovation Organization.

Chit, A. et al., 2015. The Opportunity Cost of Capital: Development of New Pharmaceuticals. *Inquiry: A Journal of Medical Care Organization, Provision, and Financing,* Volume 52, p. 0046958015584641. doi: 10.1177/0046958015584641.

Chit, A. et al., 2014. Toward More Specific and Transparent Research and Development Costs: The Case of Seasonal Influenza Vaccines. *Vaccine,* Volume 32, p. 3336–3340.

Cutting Edge Information, LLC, 2013. *Clinical Development and Trial Operations – Protocol Design and Cost per Patient Benchmarks,* Research Triangle Park, NC: Cutting Edge Information, LLC.

Damodaran Online, 2018. *Data: Archives.* [Online]
Available at:
http://people.stern.nyu.edu/adamodar/New_Home_Page/dataarchived.html
[Accessed 12 November 2019].

Damodaran Online, 2019. *Cost of Capital by Sector (US).* [Online]
Available at:
http://people.stern.nyu.edu/adamodar/New_Home_Page/datafile/wacc.htm
[Accessed 12 November 2019].

DiMasi, J. A., Grabowski, H. G. & Hansen, R. W., 2016. Innovation in the pharmaceutical industry: new estimates of R&D costs. *Journal of health economics,* Volume 47, pp. 20-33.

DiMasi, J., Feldman, L., Seckler, A. & Wilson, A., 2010. Trends in Risks Associated With New Drug Development: Success Rates for Investigational Drugs. *Clnical Pharmacology & Therapeutics,* 87(3), pp. 272-277.

DiMasi, J. & Grabowski, H., 2007. The cost of biopharmaceutical R&D: is biotech different?. *Managerial and Decision Economics,* 28(4-5), pp. 469-479.

DiMasi, J., Grabowski, H. & Vernon, J., 2004. R&D costs and returns by therapeutic category. *Drug Information Journal,* 38(3), pp. 211-223.

DiMasi, J., Hansen, R. G. H. & Lasagna, L., 1991. Cost of innovation in the pharmaceutical industry. *Journal of Health Economics,* Volume 10, pp. 107-142.

DiMasi, J., Hansen, R. & Grabowski, H., 2003. The Price of Innovation: New Estimates of Drug Development Costs. *Journal of Health Economics,* 22(2), pp. 151-185.

Eastern Research Group, Inc., 2022. *Evaluating the Potential Impacts of Different Clinical Trial Strategies on Drug, Preventive Vaccine, and Therapeutic Complex Medical Device Development,* Washington, DC: US Department of Health and Human Services, Office of the Assistant Secretary for Planning and Evaluation.

Eastern Research Group, Inc., 2022. *Evaluating the Potential Impacts of Different Clinical Trial Strategies on Drug, Preventive Vaccine, and Therapeutic Complex Medical Device Development,* Washington, DC: US Department of Health and Human Services, Office of the Assistant Secretary for Planning and Evaluation.

Federal Register, 2018. *Prescription Drug User Fee Rates for Fiscal Year 2019.* [Online] Available at: https://www.federalregister.gov/documents/2018/08/01/2018-16387/prescription-drug-user-fee-rates-for-fiscal-year-2019 [Accessed 25 August 2024].

Gouglas, D. et al., 2018. Estimating the cost of vaccine development against epidemic infectious diseases: A cost minimization study. *The Lancet,* Volume 6, pp. e1386-e1396.

Harrington, S., 2012. Cost of Capital for Pharmaceutical, Biotechnology, and Medical Device Firms. In: P. Danzon & S. Nicholson, eds. *The Oxford Handbook of the Economics of the Biopharmaceutical Industry.* New York: Oxford University Press, pp. 75-99.

Hsiue, E., Moore, T. & Alexander, G., 2020. Estimated Costs of Pivotal Trials for U.S. Food and Drug Administration-approved Cancer Drugs, 2015-2017. *Clinical Trials,* 17(2), pp. 119-125. doi: 10.1177/1740774520907609.

Jayasundara, K. et al., 2019. Estimating the clinical cost of drug development for orphan versus non-orphan drugs. *Orphanet Journal of Rare Diseases,* 14(1), p. 12.

Lansdowne, L. E., 2020. *Exploring the Drug Development Process.* [Online] Available at: https://www.technologynetworks.com/drug-discovery/articles/exploring-the-drug-development-process-331894 [Accessed 20 July 2020].

Light, D. & Warburton, R., 2011. Demythologizing the High Costs of Pharmaceutical Research. *BioSocieties,* Volume 6, pp. 34-50. doi: 10.1057/biosoc.2010.40.

Makower, J., Meer, A. & Denend, L., 2010. *FDA Impact on U.S. Medical Device Innovation: A Survey of over 200 Medical Technology Companies,* San Francisco, CA: Medical Device Manufacturers Association (MDMA) and National Venture Capital Association (NVCA).

Martin, L., Hutchens, M. & Hawkins, C., 2017. 2017. *Nature Reviews: Drug Discovery,* 16(March), p. 157.

Medidata Solutions, 2012. *Custom tabulation on clnical trial costs by phase and therapeutic area.* s.l.:s.n.

Mestre-Ferrandiz, J., Sussex, J. & Towse, A., 2012. *The R&D Cost of a New Medicine,* London, UK: Office of Health Economics.

Moore, T. J., Heyward, J., Anderson, G. & Alexander, G. C., 2020. Variation in the estimated costs of pivotal clinical benefit trials supporting the US approval of new therapeutic agents, 2015–2017: a cross-sectional study. *BMJ Open,* Volume 10, p. e038863.

PAREXEL International Corp., 2017. *PAREXEL Biopharmaceutical R&D Statistical Sourcebook 2017/2018.* Newton, MA: PAREXEL International Corp..

Paul, S. et al., 2010. How to Improve R&D Productivity: The Pharmaceutical Industry's Grand Challenge. *Nature Reviews: Drug Discovery,* 9(3), pp. 203-214.

Prasad, V. & Mailankody, S., 2017. Research and development spending to bring a single cancer drug to market and revenues after approval. *JAMA Internal Medicine,* 177(11), pp. 1569-1575.

Sertkaya, A., Wong, H.-H., Jessup, A. & Beleche, T., 2016. Key cost drivers of pharmaceutical clinical trials in the United States. *Clinical Trials,* 13(2), pp. 117-126.

Stergiopoulos, S., Kim, J. & Getz, K., 2013. Characterizing the Cost of Non-Clinical Development Activity - Understanding a Critical R&D Segment. *Contract Pharma*, 5 June.

U.S. Food and Drug Administration, 2016a. *Non-Inferiority Clinical Trials to Establish Effectiveness - Guidance for Industry,* Silver Spring, MD: U.S. Food and Drug Administration, Center for Drug Evaluation and Research.

U.S. Food and Drug Administration, 2018b. *The Drug Development Process.* [Online] Available at: https://www.fda.gov/patients/learn-about-drug-and-device-approvals/drug-development-process [Accessed 17 July 2020].

U.S. Food and Drug Administration, 2018j. *Transfer of Therapeutic Products to the Center for Drug Evaluation and Research (CDER).* [Online] Available at: https://www.fda.gov/about-fda/center-biologics-evaluation-and-research-cber/transfer-therapeutic-products-center-drug-evaluation-and-research-cder [Accessed 15 August 2020].

U.S. Food and Drug Administration, 2018l. *Custom query from FDA's DASH database,* Silver Spring, MD: s.n.

U.S. Food and Drug Administration, 2019d. *Custom data pull from FDA CDER's internal tracking database.* Silver Spring, MD: U.S. Food and Drug Administration.

U.S. Food and Drug Administration, 2020b. *Learn About FDA Advisory Committees.* [Online] Available at: https://www.fda.gov/patients/about-office-patient-affairs/learn-about-

fda-advisory-committees
[Accessed 28 July 2021].

U.S. Food and Drug Administration, 2021a. *Conduct of Clinical Trials of Medical Products During the COVID-19 Public Health Emergency - Guidance for Industry, Investigators, and Institutional Review Boards.* [Online]
Available at: https://www.fda.gov/media/136238/download
[Accessed 7 July 2021].

Wong, C., Siah, K. & Lo, A., 2019. Estimation of Clinical Trial Success Rates and Related Parameters. *Biostatistics,* 20(2), pp. 273-286.

Wouters, O. J., McKee, M. & Luyten, J., 2020. Estimated research and development investment needed to bring a new medicine to market, 2009-2018. *JAMA,* 323(9), pp. 844-853.

APPENDIX A – DETAILED EXPERT ESTIMATES OF STRATEGY IMPACTS ON COST, DURATION, AND PROBABILITY OF PHASE TRANSITION SUCCESS FOR DRUGS, BY THERAPEUTIC AREA

Therapeutic Area	Phase	Element	Mobile Technologies	Simplified Clinical Trial Protocols and Reduced Amendments	Reduced SDV	Improvements in FDA Review Efficiency and Interactions	Staged Approval	Biomarkers as Surrogate Endpoints	Electronic Health Records	Patient Registries	Adaptive Design	Standardized Contracts
Anti-infective	Non-clinical	Cost	-1%	-3%	-1%	-1%	0%	-5%	-1%	0%	0%	-4%
	Non-clinical	Success Likelihood	0%	0%	0%	3%	0%	5%	0%	0%	0%	0%
	Non-clinical	Duration	0%	-2%	0%	0%	0%	-2%	-1%	0%	0%	-5%
	Phase 1	Cost	-2%	-5%	-4%	-2%	0%	-3%	-1%	-4%	5%	-5%
	Phase 1	Success Likelihood	1%	1%	0%	2%	1%	5%	1%	0%	4%	0%
	Phase 1	Duration	-2%	-5%	-2%	-2%	0%	-2%	-3%	-5%	6%	-8%
	Phase 2	Cost	-7%	-9%	-8%	-4%	-1%	-5%	-5%	-4%	-2%	-6%
	Phase 2	Success Likelihood	4%	3%	0%	9%	6%	2%	1%	0%	12%	0%
	Phase 2	Duration	-5%	-7%	-4%	-3%	-1%	-6%	-4%	-5%	0%	-8%
	Phase 3	Cost	-13%	-12%	-15%	-10%	-10%	-9%	-9%	-5%	-8%	-8%
	Phase 3	Success Likelihood	4%	5%	0%	13%	5%	5%	2%	1%	9%	0%
	Phase 3	Duration	-8%	-8%	-9%	-9%	-8%	-7%	-8%	-5%	-9%	-10%
	Phase 3L	Cost	-13%	-12%	-15%	-10%	-10%	-9%	-9%	-7%	-8%	-8%
	Phase 3L	Success Likelihood	4%	5%	0%	13%	5%	5%	2%	1%	9%	0%
	Phase 3L	Duration	-8%	-8%	-9%	-9%	-8%	-7%	-8%	-7%	-9%	-10%
	Phase 3N	Cost	-13%	-12%	-15%	-10%	-10%	-9%	-9%	-5%	-8%	-8%
	Phase 3N	Success Likelihood	4%	5%	0%	13%	5%	5%	2%	1%	9%	0%
	Phase 3N	Duration	-8%	-8%	-9%	-9%	-8%	-7%	-8%	-5%	-9%	-10%
	FDA Submission	Cost	-5%	-3%	-10%	-2%	-5%	-2%	-4%	-4%	-1%	-3%
	FDA Submission	Success Likelihood	1%	1%	0%	5%	4%	1%	1%	0%	5%	0%
	FDA Submission	Duration	-1%	-3%	-6%	-1%	-4%	-2%	-6%	-4%	-2%	-5%
	Phase 4	Cost	-18%	-9%	-14%	-5%	-1%	-2%	-14%	-6%	-3%	-6%
	Phase 4	Duration	-8%	-6%	-6%	-3%	-1%	-1%	-12%	-7%	-3%	-8%
Cardiovascular	Non-clinical	Cost	-1%	-3%	-4%	-1%	0%	-3%	-1%	0%	0%	-5%
	Non-clinical	Success Likelihood	0%	0%	-5%	3%	0%	4%	0%	0%	0%	1%
	Non-clinical	Duration	0%	-2%	-4%	0%	0%	-1%	-1%	0%	0%	-6%
	Phase 1	Cost	-2%	-8%	-7%	-3%	0%	-3%	-1%	-4%	5%	-7%

Therapeutic Area	Phase	Element	Mobile Technologies	Simplified Clinical Trial Protocols and Reduced Amendments	Reduced SDV	Improvements in FDA Review Efficiency and Interactions	Staged Approval	Biomarkers as Surrogate Endpoints	Electronic Health Records	Patient Registries	Adaptive Design	Standardized Contracts
	Phase 1	Success Likelihood	1%	1%	-5%	5%	1%	5%	1%	0%	3%	1%
	Phase 1	Duration	-2%	-5%	-5%	-3%	0%	-1%	-4%	-4%	5%	-8%
	Phase 2	Cost	-9%	-11%	-11%	-6%	-1%	-1%	-5%	-4%	-2%	-8%
	Phase 2	Success Likelihood	4%	3%	-3%	12%	6%	1%	1%	0%	11%	2%
	Phase 2	Duration	-6%	-8%	-7%	-5%	-1%	-2%	-4%	-4%	0%	-10%
	Phase 3	Cost	-14%	-16%	-18%	-12%	-10%	-4%	-8%	-5%	-7%	-10%
	Phase 3	Success Likelihood	5%	8%	-3%	14%	5%	3%	2%	1%	8%	2%
	Phase 3	Duration	-9%	-11%	-12%	-9%	-7%	-3%	-8%	-5%	-7%	-12%
	Phase 3L	Cost	-14%	-16%	-18%	-12%	-10%	-4%	-9%	-6%	-7%	-10%
	Phase 3L	Success Likelihood	5%	8%	-3%	14%	5%	3%	2%	1%	8%	2%
	Phase 3L	Duration	-9%	-11%	-12%	-9%	-7%	-3%	-9%	-7%	-7%	-12%
	Phase 3N	Cost	-14%	-16%	-18%	-12%	-10%	-4%	-8%	-5%	-7%	-10%
	Phase 3N	Success Likelihood	5%	8%	-3%	14%	5%	3%	2%	1%	8%	2%
	Phase 3N	Duration	-9%	-11%	-12%	-9%	-7%	-3%	-8%	-5%	-7%	-12%
	FDA Submission	Cost	-6%	-6%	-13%	-5%	-4%	-2%	-5%	-3%	-2%	-6%
	FDA Submission	Success Likelihood	2%	4%	-3%	5%	3%	1%	1%	0%	5%	1%
	FDA Submission	Duration	-2%	-6%	-9%	-2%	-4%	-2%	-7%	-4%	-2%	-7%
	Phase 4	Cost	-21%	-15%	-15%	-8%	-1%	-2%	-17%	-10%	-3%	-9%
	Phase 4	Duration	-9%	-10%	-7%	-4%	-1%	-1%	-12%	-8%	-3%	-10%
Central Nervous System	Non-clinical	Cost	-1%	-4%	-1%	-1%	0%	-4%	-1%	0%	0%	-4%
	Non-clinical	Success Likelihood	0%	0%	0%	4%	0%	5%	0%	0%	0%	0%
	Non-clinical	Duration	0%	-3%	0%	0%	0%	-2%	-1%	0%	0%	-5%
	Phase 1	Cost	-3%	-5%	-5%	-2%	0%	-3%	0%	-5%	6%	-6%
	Phase 1	Success Likelihood	2%	1%	0%	2%	2%	6%	2%	0%	4%	0%
	Phase 1	Duration	-3%	-5%	-2%	-2%	0%	-2%	-3%	-5%	7%	-7%
	Phase 2	Cost	-8%	-9%	-10%	-4%	-2%	-1%	-5%	-5%	-1%	-7%
	Phase 2	Success Likelihood	4%	4%	0%	10%	7%	2%	2%	0%	14%	0%
	Phase 2	Duration	-6%	-8%	-5%	-3%	-2%	-3%	-4%	-5%	1%	-9%
	Phase 3	Cost	-15%	-13%	-18%	-10%	-12%	-5%	-8%	-6%	-8%	-9%
	Phase 3	Success Likelihood	5%	6%	0%	13%	6%	4%	3%	1%	10%	0%
	Phase 3	Duration	-9%	-9%	-10%	-8%	-9%	-3%	-8%	-6%	-9%	-12%

Therapeutic Area	Phase	Element	Mobile Technologies	Simplified Clinical Trial Protocols and Reduced Amendments	Reduced SDV	Improvements in FDA Review Efficiency and Interactions	Staged Approval	Biomarkers as Surrogate Endpoints	Electronic Health Records	Patient Registries	Adaptive Design	Standardized Contracts
	Phase 3L	Cost	-15%	-13%	-18%	-10%	-12%	-5%	-9%	-8%	-8%	-9%
	Phase 3L	Success Likelihood	5%	6%	0%	13%	6%	4%	3%	2%	10%	0%
	Phase 3L	Duration	-9%	-9%	-10%	-8%	-9%	-3%	-9%	-8%	-9%	-12%
	Phase 3N	Cost	-15%	-13%	-18%	-10%	-12%	-5%	-8%	-6%	-8%	-9%
	Phase 3N	Success Likelihood	5%	6%	0%	13%	6%	4%	3%	1%	10%	0%
	Phase 3N	Duration	-9%	-9%	-10%	-8%	-9%	-3%	-8%	-6%	-9%	-12%
	FDA Submission	Cost	-6%	-3%	-12%	-2%	-5%	-3%	-5%	-4%	-1%	-3%
	FDA Submission	Success Likelihood	1%	1%	0%	6%	4%	2%	1%	0%	6%	0%
	FDA Submission	Duration	-1%	-3%	-7%	-1%	-5%	-3%	-7%	-5%	-2%	-5%
	Phase 4	Cost	-21%	-10%	-17%	-5%	-1%	-3%	-15%	-7%	-3%	-8%
	Phase 4	Duration	-9%	-7%	-7%	-3%	-1%	-2%	-13%	-8%	-3%	-9%
Dermatology	Non-clinical	Cost	-1%	-4%	-1%	-1%	0%	-4%	-1%	0%	0%	-4%
	Non-clinical	Success Likelihood	0%	0%	0%	4%	0%	5%	0%	0%	0%	0%
	Non-clinical	Duration	0%	-3%	0%	0%	0%	-2%	-1%	0%	0%	-5%
	Phase 1	Cost	-3%	-5%	-5%	-2%	0%	-3%	0%	-5%	6%	-6%
	Phase 1	Success Likelihood	2%	1%	0%	2%	2%	6%	2%	0%	4%	0%
	Phase 1	Duration	-3%	-5%	-2%	-2%	0%	-2%	-3%	-5%	7%	-7%
	Phase 2	Cost	-8%	-9%	-10%	-4%	-2%	-1%	-5%	-5%	-1%	-7%
	Phase 2	Success Likelihood	4%	4%	0%	10%	7%	2%	2%	0%	14%	0%
	Phase 2	Duration	-6%	-8%	-5%	-3%	-2%	-3%	-4%	-5%	1%	-9%
	Phase 3	Cost	-15%	-13%	-18%	-10%	-12%	-5%	-8%	-6%	-8%	-9%
	Phase 3	Success Likelihood	5%	6%	0%	13%	6%	4%	3%	1%	10%	0%
	Phase 3	Duration	-9%	-9%	-10%	-8%	-9%	-3%	-8%	-6%	-9%	-12%
	Phase 3L	Cost	-15%	-13%	-18%	-10%	-12%	-5%	-9%	-8%	-8%	-9%
	Phase 3L	Success Likelihood	5%	6%	0%	13%	6%	4%	3%	2%	10%	0%
	Phase 3L	Duration	-9%	-9%	-10%	-8%	-9%	-3%	-9%	-8%	-9%	-12%
	Phase 3N	Cost	-15%	-13%	-18%	-10%	-12%	-5%	-8%	-6%	-8%	-9%
	Phase 3N	Success Likelihood	5%	6%	0%	13%	6%	4%	3%	1%	10%	0%
	Phase 3N	Duration	-9%	-9%	-10%	-8%	-9%	-3%	-8%	-6%	-9%	-12%
	FDA Submission	Cost	-6%	-3%	-12%	-2%	-5%	-3%	-5%	-4%	-1%	-3%
	FDA Submission	Success Likelihood	1%	1%	0%	6%	4%	2%	1%	0%	6%	0%

Therapeutic Area	Phase	Element	Mobile Technologies	Simplified Clinical Trial Protocols and Reduced Amendments	Reduced SDV	Improvements in FDA Review Efficiency and Interactions	Staged Approval	Biomarkers as Surrogate Endpoints	Electronic Health Records	Patient Registries	Adaptive Design	Standardized Contracts
	FDA Submission	Duration	-1%	-3%	-7%	-1%	-5%	-3%	-7%	-5%	-2%	-5%
	Phase 4	Cost	-21%	-10%	-17%	-5%	-1%	-3%	-15%	-7%	-3%	-8%
	Phase 4	Duration	-9%	-7%	-7%	-3%	-1%	-2%	-13%	-8%	-3%	-9%
Endocrine	Non-clinical	Cost	-1%	-3%	-1%	-1%	0%	-4%	-1%	0%	0%	-4%
	Non-clinical	Success Likelihood	0%	0%	0%	3%	0%	5%	0%	0%	0%	0%
	Non-clinical	Duration	0%	-2%	0%	0%	0%	-2%	-1%	0%	0%	-5%
	Phase 1	Cost	-2%	-7%	-5%	-2%	0%	-3%	-1%	-5%	5%	-5%
	Phase 1	Success Likelihood	2%	1%	0%	2%	2%	5%	2%	0%	4%	0%
	Phase 1	Duration	-2%	-6%	-2%	-2%	0%	-2%	-5%	-5%	6%	-7%
	Phase 2	Cost	-9%	-11%	-9%	-5%	-2%	-1%	-6%	-5%	-2%	-7%
	Phase 2	Success Likelihood	5%	3%	0%	10%	7%	2%	2%	0%	13%	0%
	Phase 2	Duration	-7%	-9%	-5%	-4%	-2%	-2%	-5%	-5%	1%	-9%
	Phase 3	Cost	-15%	-14%	-17%	-12%	-11%	-5%	-10%	-6%	-8%	-9%
	Phase 3	Success Likelihood	6%	6%	0%	12%	6%	4%	2%	1%	9%	0%
	Phase 3	Duration	-10%	-10%	-10%	-9%	-8%	-3%	-9%	-6%	-8%	-12%
	Phase 3L	Cost	-15%	-14%	-17%	-12%	-11%	-5%	-10%	-7%	-8%	-9%
	Phase 3L	Success Likelihood	6%	6%	0%	12%	6%	4%	2%	2%	9%	0%
	Phase 3L	Duration	-10%	-10%	-10%	-9%	-8%	-3%	-10%	-8%	-8%	-12%
	Phase 3N	Cost	-15%	-14%	-17%	-12%	-11%	-5%	-10%	-6%	-8%	-9%
	Phase 3N	Success Likelihood	6%	6%	0%	12%	6%	4%	2%	1%	9%	0%
	Phase 3N	Duration	-10%	-10%	-10%	-9%	-8%	-3%	-9%	-6%	-8%	-12%
	FDA Submission	Cost	-7%	-5%	-11%	-5%	-5%	-2%	-6%	-4%	-2%	-4%
	FDA Submission	Success Likelihood	2%	1%	0%	5%	3%	2%	1%	0%	5%	0%
	FDA Submission	Duration	-3%	-4%	-7%	-3%	-5%	-2%	-8%	-4%	-2%	-6%
	Phase 4	Cost	-22%	-11%	-15%	-9%	-1%	-2%	-20%	-11%	-3%	-8%
	Phase 4	Duration	-10%	-8%	-7%	-5%	-1%	-2%	-14%	-9%	-3%	-9%
Gastrointestinal	Non-clinical	Cost	-1%	-4%	-1%	-1%	0%	-4%	-1%	0%	0%	-4%
	Non-clinical	Success Likelihood	0%	0%	0%	4%	0%	5%	0%	0%	0%	0%
	Non-clinical	Duration	0%	-3%	0%	0%	0%	-2%	-1%	0%	0%	-5%
	Phase 1	Cost	-3%	-5%	-5%	-2%	0%	-3%	0%	-5%	6%	-6%
	Phase 1	Success Likelihood	2%	1%	0%	2%	2%	6%	2%	0%	4%	0%

Therapeutic Area	Phase	Element	Mobile Technologies	Simplified Clinical Trial Protocols and Reduced Amendments	Reduced SDV	Improvements in FDA Review Efficiency and Interactions	Staged Approval	Biomarkers as Surrogate Endpoints	Electronic Health Records	Patient Registries	Adaptive Design	Standardized Contracts
	Phase 1	Duration	-3%	-5%	-2%	-2%	0%	-2%	-3%	-5%	7%	-7%
	Phase 2	Cost	-8%	-9%	-10%	-4%	-2%	-1%	-5%	-5%	-1%	-7%
	Phase 2	Success Likelihood	4%	4%	0%	10%	7%	2%	2%	0%	14%	0%
	Phase 2	Duration	-6%	-8%	-5%	-3%	-2%	-3%	-4%	-5%	1%	-9%
	Phase 3	Cost	-15%	-13%	-18%	-10%	-12%	-5%	-8%	-6%	-8%	-9%
	Phase 3	Success Likelihood	5%	6%	0%	13%	6%	4%	3%	1%	10%	0%
	Phase 3	Duration	-9%	-9%	-10%	-8%	-9%	-3%	-8%	-6%	-9%	-12%
	Phase 3L	Cost	-15%	-13%	-18%	-10%	-12%	-5%	-9%	-8%	-8%	-9%
	Phase 3L	Success Likelihood	5%	6%	0%	13%	6%	4%	3%	2%	10%	0%
	Phase 3L	Duration	-9%	-9%	-10%	-8%	-9%	-3%	-9%	-8%	-9%	-12%
	Phase 3N	Cost	-15%	-13%	-18%	-10%	-12%	-5%	-8%	-6%	-8%	-9%
	Phase 3N	Success Likelihood	5%	6%	0%	13%	6%	4%	3%	1%	10%	0%
	Phase 3N	Duration	-9%	-9%	-10%	-8%	-9%	-3%	-8%	-6%	-9%	-12%
	FDA Submission	Cost	-6%	-3%	-12%	-2%	-5%	-3%	-5%	-4%	-1%	-3%
	FDA Submission	Success Likelihood	1%	1%	0%	6%	4%	2%	1%	0%	6%	0%
	FDA Submission	Duration	-1%	-3%	-7%	-1%	-5%	-3%	-7%	-5%	-2%	-5%
	Phase 4	Cost	-21%	-10%	-17%	-5%	-1%	-3%	-15%	-7%	-3%	-8%
	Phase 4	Duration	-9%	-7%	-7%	-3%	-1%	-2%	-13%	-8%	-3%	-9%
Genitourinary System	Non-clinical	Cost	-1%	-4%	-1%	-1%	0%	-4%	-1%	0%	0%	-4%
	Non-clinical	Success Likelihood	0%	0%	0%	4%	0%	5%	0%	0%	0%	0%
	Non-clinical	Duration	0%	-3%	0%	0%	0%	-2%	-1%	0%	0%	-5%
	Phase 1	Cost	-3%	-5%	-5%	-2%	0%	-3%	0%	-5%	6%	-6%
	Phase 1	Success Likelihood	2%	1%	0%	2%	2%	6%	2%	0%	4%	0%
	Phase 1	Duration	-3%	-5%	-2%	-2%	0%	-2%	-3%	-5%	7%	-7%
	Phase 2	Cost	-8%	-9%	-10%	-4%	-2%	-1%	-5%	-5%	-1%	-7%
	Phase 2	Success Likelihood	4%	4%	0%	10%	7%	2%	2%	0%	14%	0%
	Phase 2	Duration	-6%	-8%	-5%	-3%	-2%	-3%	-4%	-5%	1%	-9%
	Phase 3	Cost	-15%	-13%	-18%	-10%	-12%	-5%	-8%	-6%	-8%	-9%
	Phase 3	Success Likelihood	5%	6%	0%	13%	6%	4%	3%	1%	10%	0%
	Phase 3	Duration	-9%	-9%	-10%	-8%	-9%	-3%	-8%	-6%	-9%	-12%
	Phase 3L	Cost	-15%	-13%	-18%	-10%	-12%	-5%	-9%	-8%	-8%	-9%

Therapeutic Area	Phase	Element	Mobile Technologies	Simplified Clinical Trial Protocols and Reduced Amendments	Reduced SDV	Improvements in FDA Review Efficiency and Interactions	Staged Approval	Biomarkers as Surrogate Endpoints	Electronic Health Records	Patient Registries	Adaptive Design	Standardized Contracts
	Phase 3L	Success Likelihood	5%	6%	0%	13%	6%	4%	3%	2%	10%	0%
	Phase 3L	Duration	-9%	-9%	-10%	-8%	-9%	-3%	-9%	-8%	-9%	-12%
	Phase 3N	Cost	-15%	-13%	-18%	-10%	-12%	-5%	-8%	-6%	-8%	-9%
	Phase 3N	Success Likelihood	5%	6%	0%	13%	6%	4%	3%	1%	10%	0%
	Phase 3N	Duration	-9%	-9%	-10%	-8%	-9%	-3%	-8%	-6%	-9%	-12%
	FDA Submission	Cost	-6%	-3%	-12%	-2%	-5%	-3%	-5%	-4%	-1%	-3%
	FDA Submission	Success Likelihood	1%	1%	0%	6%	4%	2%	1%	0%	6%	0%
	FDA Submission	Duration	-1%	-3%	-7%	-1%	-5%	-3%	-7%	-5%	-2%	-5%
	Phase 4	Cost	-21%	-10%	-17%	-5%	-1%	-3%	-15%	-7%	-3%	-8%
	Phase 4	Duration	-9%	-7%	-7%	-3%	-1%	-2%	-13%	-8%	-3%	-9%
Hematology	Non-clinical	Cost	-1%	-4%	-1%	-1%	0%	-4%	-1%	0%	0%	-4%
	Non-clinical	Success Likelihood	0%	0%	0%	4%	0%	5%	0%	0%	0%	0%
	Non-clinical	Duration	0%	-3%	0%	0%	0%	-2%	-1%	0%	0%	-5%
	Phase 1	Cost	-3%	-5%	-5%	-2%	0%	-3%	0%	-5%	6%	-6%
	Phase 1	Success Likelihood	2%	1%	0%	2%	2%	6%	2%	0%	4%	0%
	Phase 1	Duration	-3%	-5%	-2%	-2%	0%	-2%	-3%	-5%	7%	-7%
	Phase 2	Cost	-8%	-9%	-10%	-4%	-2%	-1%	-5%	-5%	-1%	-7%
	Phase 2	Success Likelihood	4%	4%	0%	10%	7%	2%	2%	0%	14%	0%
	Phase 2	Duration	-6%	-8%	-5%	-3%	-2%	-3%	-4%	-5%	1%	-9%
	Phase 3	Cost	-15%	-13%	-18%	-10%	-12%	-5%	-8%	-6%	-8%	-9%
	Phase 3	Success Likelihood	5%	6%	0%	13%	6%	4%	3%	1%	10%	0%
	Phase 3	Duration	-9%	-9%	-10%	-8%	-9%	-3%	-8%	-6%	-9%	-12%
	Phase 3L	Cost	-15%	-13%	-18%	-10%	-12%	-5%	-9%	-8%	-8%	-9%
	Phase 3L	Success Likelihood	5%	6%	0%	13%	6%	4%	3%	2%	10%	0%
	Phase 3L	Duration	-9%	-9%	-10%	-8%	-9%	-3%	-9%	-8%	-9%	-12%
	Phase 3N	Cost	-15%	-13%	-18%	-10%	-12%	-5%	-8%	-6%	-8%	-9%
	Phase 3N	Success Likelihood	5%	6%	0%	13%	6%	4%	3%	1%	10%	0%
	Phase 3N	Duration	-9%	-9%	-10%	-8%	-9%	-3%	-8%	-6%	-9%	-12%
	FDA Submission	Cost	-6%	-3%	-12%	-2%	-5%	-3%	-5%	-4%	-1%	-3%
	FDA Submission	Success Likelihood	1%	1%	0%	6%	4%	2%	1%	0%	6%	0%
	FDA Submission	Duration	-1%	-3%	-7%	-1%	-5%	-3%	-7%	-5%	-2%	-5%

Therapeutic Area	Phase	Element	Mobile Technologies	Simplified Clinical Trial Protocols and Reduced Amendments	Reduced SDV	Improvements in FDA Review Efficiency and Interactions	Staged Approval	Biomarkers as Surrogate Endpoints	Electronic Health Records	Patient Registries	Adaptive Design	Standardized Contracts
	Phase 4	Cost	-21%	-10%	-17%	-5%	-1%	-3%	-15%	-7%	-3%	-8%
	Phase 4	Duration	-9%	-7%	-7%	-3%	-1%	-2%	-13%	-8%	-3%	-9%
Immunomodulation	Non-clinical	Cost	-1%	-3%	-1%	-1%	0%	-5%	-1%	0%	0%	-4%
	Non-clinical	Success Likelihood	0%	0%	0%	3%	0%	5%	0%	0%	0%	0%
	Non-clinical	Duration	0%	-2%	0%	0%	0%	-2%	-1%	0%	0%	-5%
	Phase 1	Cost	-2%	-5%	-5%	-2%	0%	-3%	0%	-5%	5%	-5%
	Phase 1	Success Likelihood	2%	1%	0%	2%	2%	5%	2%	0%	4%	0%
	Phase 1	Duration	-2%	-5%	-2%	-2%	0%	-2%	-3%	-5%	6%	-7%
	Phase 2	Cost	-8%	-9%	-9%	-3%	-2%	-2%	-4%	-5%	-2%	-6%
	Phase 2	Success Likelihood	4%	3%	0%	10%	7%	2%	2%	0%	13%	0%
	Phase 2	Duration	-6%	-8%	-5%	-2%	-2%	-3%	-4%	-5%	0%	-8%
	Phase 3	Cost	-14%	-13%	-17%	-9%	-11%	-5%	-8%	-6%	-8%	-8%
	Phase 3	Success Likelihood	4%	6%	0%	12%	6%	4%	2%	1%	10%	0%
	Phase 3	Duration	-9%	-9%	-10%	-8%	-8%	-4%	-8%	-6%	-9%	-11%
	Phase 3L	Cost	-14%	-13%	-17%	-9%	-11%	-5%	-8%	-7%	-8%	-8%
	Phase 3L	Success Likelihood	4%	6%	0%	12%	6%	4%	2%	2%	10%	0%
	Phase 3L	Duration	-9%	-9%	-10%	-8%	-8%	-4%	-8%	-8%	-9%	-11%
	Phase 3N	Cost	-14%	-13%	-17%	-9%	-11%	-5%	-8%	-6%	-8%	-8%
	Phase 3N	Success Likelihood	4%	6%	0%	12%	6%	4%	2%	1%	10%	0%
	Phase 3N	Duration	-9%	-9%	-10%	-8%	-8%	-4%	-8%	-6%	-9%	-11%
	FDA Submission	Cost	-5%	-3%	-11%	-2%	-5%	-2%	-4%	-4%	-1%	-3%
	FDA Submission	Success Likelihood	1%	1%	0%	6%	3%	2%	1%	0%	6%	0%
	FDA Submission	Duration	-1%	-3%	-7%	-2%	-5%	-2%	-7%	-4%	-2%	-5%
	Phase 4	Cost	-19%	-10%	-15%	-5%	-1%	-2%	-13%	-7%	-3%	-7%
	Phase 4	Duration	-8%	-6%	-7%	-3%	-1%	-2%	-12%	-7%	-3%	-8%
Oncology	Non-clinical	Cost	-1%	-3%	-1%	-1%	0%	-3%	-1%	0%	0%	-3%
	Non-clinical	Success Likelihood	0%	0%	0%	3%	0%	7%	0%	0%	0%	0%
	Non-clinical	Duration	0%	-2%	0%	0%	0%	-1%	-1%	0%	0%	-4%
	Phase 1	Cost	-2%	-5%	-4%	-2%	0%	-2%	0%	-4%	3%	-5%
	Phase 1	Success Likelihood	1%	1%	0%	2%	1%	7%	1%	0%	5%	0%
	Phase 1	Duration	-2%	-6%	-2%	-2%	0%	-1%	-4%	-4%	3%	-7%

Therapeutic Area	Phase	Element	Mobile Technologies	Simplified Clinical Trial Protocols and Reduced Amendments	Reduced SDV	Improvements in FDA Review Efficiency and Interactions	Staged Approval	Biomarkers as Surrogate Endpoints	Electronic Health Records	Patient Registries	Adaptive Design	Standardized Contracts
	Phase 2	Cost	-7%	-9%	-8%	-4%	-1%	-1%	-4%	-4%	-3%	-6%
	Phase 2	Success Likelihood	4%	4%	0%	9%	6%	2%	1%	0%	13%	0%
	Phase 2	Duration	-5%	-9%	-4%	-3%	-1%	-2%	-5%	-4%	-2%	-8%
	Phase 3	Cost	-13%	-12%	-15%	-8%	-12%	-5%	-7%	-5%	-7%	-7%
	Phase 3	Success Likelihood	4%	6%	0%	11%	8%	4%	2%	1%	8%	0%
	Phase 3	Duration	-8%	-9%	-9%	-8%	-11%	-4%	-8%	-5%	-8%	-10%
	Phase 3L	Cost	-13%	-12%	-15%	-8%	-12%	-5%	-7%	-6%	-7%	-7%
	Phase 3L	Success Likelihood	4%	6%	0%	11%	8%	4%	2%	1%	8%	0%
	Phase 3L	Duration	-8%	-9%	-9%	-8%	-11%	-4%	-8%	-7%	-8%	-10%
	Phase 3N	Cost	-13%	-12%	-15%	-8%	-12%	-5%	-7%	-5%	-7%	-7%
	Phase 3N	Success Likelihood	4%	6%	0%	11%	8%	4%	2%	1%	8%	0%
	Phase 3N	Duration	-8%	-9%	-9%	-8%	-11%	-4%	-8%	-5%	-8%	-10%
	FDA Submission	Cost	-6%	-4%	-10%	-2%	-4%	-2%	-4%	-3%	-1%	-3%
	FDA Submission	Success Likelihood	1%	1%	0%	5%	4%	1%	1%	0%	5%	0%
	FDA Submission	Duration	-2%	-3%	-6%	-3%	-4%	-2%	-7%	-4%	-2%	-5%
	Phase 4	Cost	-19%	-9%	-15%	-4%	-1%	-2%	-12%	-6%	-2%	-6%
	Phase 4	Duration	-9%	-6%	-6%	-3%	-1%	-1%	-12%	-6%	-3%	-8%
Ophthalmology	Non-clinical	Cost	-1%	-4%	-1%	-1%	0%	-4%	-1%	0%	0%	-4%
	Non-clinical	Success Likelihood	0%	0%	0%	4%	0%	5%	0%	0%	0%	0%
	Non-clinical	Duration	0%	-3%	0%	0%	0%	-2%	-1%	0%	0%	-5%
	Phase 1	Cost	-3%	-5%	-5%	-2%	0%	-3%	0%	-5%	6%	-6%
	Phase 1	Success Likelihood	2%	1%	0%	2%	2%	6%	2%	0%	4%	0%
	Phase 1	Duration	-3%	-5%	-2%	-2%	0%	-2%	-3%	-5%	7%	-7%
	Phase 2	Cost	-8%	-9%	-10%	-4%	-2%	-1%	-5%	-5%	-1%	-7%
	Phase 2	Success Likelihood	4%	4%	0%	10%	7%	2%	2%	0%	14%	0%
	Phase 2	Duration	-6%	-8%	-5%	-3%	-2%	-3%	-4%	-5%	1%	-9%
	Phase 3	Cost	-15%	-13%	-18%	-10%	-12%	-5%	-8%	-6%	-8%	-9%
	Phase 3	Success Likelihood	5%	6%	0%	13%	6%	4%	3%	1%	10%	0%
	Phase 3	Duration	-9%	-9%	-10%	-8%	-9%	-3%	-8%	-6%	-9%	-12%
	Phase 3L	Cost	-15%	-13%	-18%	-10%	-12%	-5%	-9%	-8%	-8%	-9%
	Phase 3L	Success Likelihood	5%	6%	0%	13%	6%	4%	3%	2%	10%	0%

Therapeutic Area	Phase	Element	Mobile Technologies	Simplified Clinical Trial Protocols and Reduced Amendments	Reduced SDV	Improvements in FDA Review Efficiency and Interactions	Staged Approval	Biomarkers as Surrogate Endpoints	Electronic Health Records	Patient Registries	Adaptive Design	Standardized Contracts
	Phase 3L	Duration	-9%	-9%	-10%	-8%	-9%	-3%	-9%	-8%	-9%	-12%
	Phase 3N	Cost	-15%	-13%	-18%	-10%	-12%	-5%	-8%	-6%	-8%	-9%
	Phase 3N	Success Likelihood	5%	6%	0%	13%	6%	4%	3%	1%	10%	0%
	Phase 3N	Duration	-9%	-9%	-10%	-8%	-9%	-3%	-8%	-6%	-9%	-12%
	FDA Submission	Cost	-6%	-3%	-12%	-2%	-5%	-3%	-5%	-4%	-1%	-3%
	FDA Submission	Success Likelihood	1%	1%	0%	6%	4%	2%	1%	0%	6%	0%
	FDA Submission	Duration	-1%	-3%	-7%	-1%	-5%	-3%	-7%	-5%	-2%	-5%
	Phase 4	Cost	-21%	-10%	-17%	-5%	-1%	-3%	-15%	-7%	-3%	-8%
	Phase 4	Duration	-9%	-7%	-7%	-3%	-1%	-2%	-13%	-8%	-3%	-9%
Pain and Anesthesia	Non-clinical	Cost	-1%	-3%	-1%	-1%	0%	-4%	-1%	0%	0%	-4%
	Non-clinical	Success Likelihood	0%	0%	0%	3%	0%	5%	0%	0%	0%	0%
	Non-clinical	Duration	0%	-2%	0%	0%	0%	-2%	-1%	0%	0%	-5%
	Phase 1	Cost	-2%	-7%	-5%	-2%	0%	-3%	0%	-5%	5%	-5%
	Phase 1	Success Likelihood	2%	1%	0%	2%	2%	5%	2%	0%	4%	0%
	Phase 1	Duration	-2%	-5%	-2%	-2%	0%	-2%	-3%	-5%	6%	-7%
	Phase 2	Cost	-9%	-11%	-9%	-3%	-2%	-1%	-4%	-5%	-1%	-6%
	Phase 2	Success Likelihood	4%	3%	0%	10%	7%	2%	2%	0%	13%	0%
	Phase 2	Duration	-6%	-8%	-5%	-2%	-2%	-2%	-4%	-5%	1%	-8%
	Phase 3	Cost	-15%	-14%	-17%	-9%	-11%	-5%	-8%	-6%	-7%	-8%
	Phase 3	Success Likelihood	4%	6%	0%	12%	6%	4%	2%	1%	9%	0%
	Phase 3	Duration	-9%	-9%	-10%	-8%	-8%	-3%	-8%	-6%	-8%	-11%
	Phase 3L	Cost	-15%	-14%	-17%	-9%	-11%	-5%	-8%	-7%	-7%	-8%
	Phase 3L	Success Likelihood	4%	6%	0%	12%	6%	4%	2%	2%	9%	0%
	Phase 3L	Duration	-9%	-9%	-10%	-8%	-8%	-3%	-8%	-8%	-8%	-11%
	Phase 3N	Cost	-15%	-14%	-17%	-9%	-11%	-5%	-8%	-6%	-7%	-8%
	Phase 3N	Success Likelihood	4%	6%	0%	12%	6%	4%	2%	1%	9%	0%
	Phase 3N	Duration	-9%	-9%	-10%	-8%	-8%	-3%	-8%	-6%	-8%	-11%
	FDA Submission	Cost	-5%	-3%	-11%	-2%	-5%	-2%	-4%	-4%	-1%	-3%
	FDA Submission	Success Likelihood	1%	1%	0%	5%	3%	2%	1%	0%	5%	0%
	FDA Submission	Duration	-1%	-3%	-7%	-1%	-5%	-2%	-7%	-4%	-2%	-5%
	Phase 4	Cost	-21%	-12%	-15%	-5%	-1%	-2%	-13%	-7%	-3%	-7%

Therapeutic Area	Phase	Element	Mobile Technologies	Simplified Clinical Trial Protocols and Reduced Amendments	Reduced SDV	Improvements in FDA Review Efficiency and Interactions	Staged Approval	Biomarkers as Surrogate Endpoints	Electronic Health Records	Patient Registries	Adaptive Design	Standardized Contracts
	Phase 4	Duration	-8%	-7%	-7%	-3%	-1%	-2%	-12%	-7%	-3%	-8%
Respiratory	Non-clinical	Cost	-1%	-3%	-1%	-1%	0%	-4%	-1%	0%	0%	-4%
	Non-clinical	Success Likelihood	0%	0%	0%	3%	0%	5%	0%	0%	0%	0%
	Non-clinical	Duration	0%	-2%	0%	0%	0%	-1%	-1%	0%	0%	-5%
	Phase 1	Cost	-3%	-6%	-5%	-2%	0%	-3%	0%	-4%	4%	-5%
	Phase 1	Success Likelihood	1%	1%	0%	3%	1%	5%	1%	0%	4%	0%
	Phase 1	Duration	-2%	-5%	-2%	-2%	0%	-1%	-3%	-5%	5%	-6%
	Phase 2	Cost	-10%	-10%	-9%	-4%	-1%	-1%	-4%	-5%	-2%	-6%
	Phase 2	Success Likelihood	4%	3%	0%	10%	6%	1%	1%	0%	13%	0%
	Phase 2	Duration	-7%	-8%	-5%	-3%	-1%	-2%	-4%	-5%	0%	-10%
	Phase 3	Cost	-15%	-13%	-16%	-9%	-12%	-4%	-7%	-5%	-7%	-7%
	Phase 3	Success Likelihood	4%	5%	0%	13%	7%	4%	2%	1%	9%	0%
	Phase 3	Duration	-10%	-8%	-9%	-8%	-10%	-3%	-8%	-6%	-8%	-13%
	Phase 3L	Cost	-15%	-13%	-16%	-9%	-12%	-4%	-8%	-7%	-7%	-7%
	Phase 3L	Success Likelihood	4%	5%	0%	13%	7%	4%	2%	1%	9%	0%
	Phase 3L	Duration	-10%	-8%	-9%	-8%	-10%	-3%	-8%	-8%	-8%	-13%
	Phase 3N	Cost	-15%	-13%	-16%	-9%	-12%	-4%	-7%	-5%	-7%	-7%
	Phase 3N	Success Likelihood	4%	5%	0%	13%	7%	4%	2%	1%	9%	0%
	Phase 3N	Duration	-10%	-8%	-9%	-8%	-10%	-3%	-8%	-6%	-8%	-13%
	FDA Submission	Cost	-6%	-3%	-11%	-2%	-6%	-2%	-4%	-4%	-1%	-3%
	FDA Submission	Success Likelihood	1%	1%	0%	6%	5%	1%	1%	0%	5%	0%
	FDA Submission	Duration	-3%	-3%	-7%	-2%	-6%	-2%	-7%	-5%	-2%	-7%
	Phase 4	Cost	-21%	-11%	-15%	-5%	1%	-2%	-13%	-6%	-3%	-6%
	Phase 4	Duration	-9%	-6%	-7%	-3%	1%	-1%	-12%	-8%	-3%	-9%

Phase 3N = Phase 3 trial for a new drug

Phase 3L = Phase 3 trial for a label expansion

Note that sponsors conduct Phase 3 trials not just to obtain an NDA or a BLA approval from FDA for a new drug but also to expand the list of indications for an already-approved drug. Our initial discussions with experts indicated that some tended to think about the latter type of trials (i.e., Phase 3 trial for a label extension for an approved drug) when evaluating the nature of the impact for a given strategy. To ensure consistency, we elicited opinions for each type of Phase 3 trial separately.