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EVALUATING THE POTENTIAL IMPACTS OF DIFFERENT CLINICAL TRIAL STRATEGIES ON DRUG, PREVENTIVE VACCINE, AND THERAPEUTIC COMPLEX MEDICAL DEVICE DEVELOPMENT

FINAL

SUBMITTED TO:
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ACA	Affordable Care Act
ACTA	Accelerated Clinical Trial Agreement
ADAPTABLE	Aspirin Dosing: A Patient-centric Trial Assessing Benefits and Long-Term Effectiveness
ALS	Amyotrophic Lateral Sclerosis
ASCI	Association of American Cancer Institutes
ASCO	American Society of Clinical Oncology
ASPE	Office of The Assistant Secretary for Planning and Evaluation
BD4BO	Big Data for Better Outcomes
BLA	Biologics License Applications
caDSR	Cancer Data Standards Repository
CDISC	Clinical Data Interchange Standards Consortium
CEO	Chief Executive Officer
CER	Comparative effectiveness research
CHAP	Cardiovascular Health Awareness Program
CMD	Complex medical device
CONSORT	Consolidated Standards for Reporting Trials
CRF	Case report form
CROs	Contract research organization
CSHARE	CDISC Shared Health and Research Electronic Library
CTSA	Clinical and Translational Science Awards
CTTI	Clinical Trials Transformation Initiative
DHHS	Department of Health and Human Services
DHT	Digital Health Technology
ECG	Electrocardiogram
eCRF	Electronic case report form
eNPV	Expected net present value
EDC	Electronic data collection
EHR	Electronic health record
EHR4CR	Electronic Health Records for Clinical Research
EMA	European Medicines Agency
ERG	Eastern Research Group, Inc.
FDA	Food and Drug Administration
FIH	First in human
FTE	Full-time equivalent
GCP	Good Clinical Practice
GHTF	Global Harmonization Task Force
GSK	GlaxoSmithKline
HIV	Human immunodeficiency virus
HMORN	HMO Research Network (now Health Care Systems Research Network [HCSRN])
ICD-9	International Classification of Diseases, Ninth Revision
ICD-9-CM	International Classification of Diseases, Ninth Revision, Clinical Modification

ICH-GCP	International Conference on Harmonization Good Clinical Practice
ICMJE	International Committee of Medical Journal Editors
IEC	International Electrotechnical Commission
IMP	Investigational Medicinal Product
IND	Investigational New Drugs
IOM	Institute of Medicine
IRB	Institutional review board
ISO	International Organization for Standardization
ITN	Immune Tolerance Network
MDUFA	Medical Device User Fee Amendments
MHRA	UK Medicines and Healthcare Products Regulatory Agency
MTD	Maximum tolerated dose
NCI	National Cancer Institute
NDA	New Drug Application
NIH	National Institutes of Health
NME	New molecular entity
NPV	Net present value
OCOC	Opportunity Cost of Capital
OCR	NIH Office of Clinical Research
OHRP	DHHS Office for Human Research Protections
PCORnet	National Patient-Centered Clinical Research Network
PCR	Polymerase chain reaction
PCTs	Pragmatic (or practical) clinical trials
PDUFA III	Prescription Drug User Fee Act, Third Authorization (Fiscal Years 2002 - 2007)
PDUFA V	Prescription Drug User Fee Act, Fifth Authorization (Fiscal Years 2013 - 2017)
PDUFA VI	Prescription Drug User Fee Act, Sixth Authorization (Fiscal Years 2018 - 2022)
PMA	Premarket Approval
POS	Probability of success
PRECIS	Pragmatic-explanatory continuum indicator summary
PRO-ACT	Pooled Resource Open-access ALS Clinical Trials
PVac	Preventive vaccine
RCT	Randomized clinical trial
REDUCE	Randomized Evaluation of Decolonization versus Universal Clearance to Eliminate
MRSA	Methicillin-Resistant Staphylococcus Aureus
SAE	Serious adverse event
SAFE-PCI	Study of Access Site for Enhancement of Percutaneous Coronary Intervention
SCAD	Spontaneous coronary artery dissection
SDV	Source data verification
SPIRIT	Standard Protocol Items: Recommendations for Interventional Trials
TASTE	Thrombus Aspiration in ST-Elevation Myocardial Infarction in Scandinavia
UDI	Unique device identifier
VHP	Voluntary Harmonization Procedure
WHO	World Health Organization

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). For complex medical devices that require a Premarket Application (PMA) submission to FDA, clinical trial costs account for roughly 51 percent of total R&D expenditures (Makower, et al., 2010). 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.

Given the continued interest in improving the efficiency of clinical trials, it is worthwhile to re-examine the potential impact different strategies could have on the cost of medical product development. Thus, the objective of this environmental scan is to identify promising clinical strategies with potential to improve medical product development efficiency, especially those that have come to focus since the 2014 study, titled *Examination of Clinical Trial Costs and Barriers for Drug Development* (Eastern Research Group, Inc., 2014), and to quantify their impact on the primary cost drivers of development, e.g., clinical study duration, cost, and phase transition success probability. The medical products this scan focuses on include drugs, preventive vaccines, and therapeutic complex medical devices.

This environmental scan, conducted from September 2016 – September 2021, examines the potential impacts of the following strategies on the cost, duration, and phase transition probability associated with drug, preventive vaccine, and therapeutic complex medical device development stages:

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

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

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

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

- **Staged approval—**Staged approval could entail granting provisional marketing approval to market a drug, complex medical device, or preventive vaccine after safety and basic efficacy have been shown, and then continuing to collect additional safety and efficacy data. This would reduce the threshold for initial approval, perhaps with a limited patient population, and then gradually expand it as more data are collected.

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

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

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

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

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

- **CDC/NIH developing epidemiological data on disease incidence (applicable to preventive vaccines only)—**This strategy would entail CDC and/or NIH collecting epidemiological data on disease incidence that is tailored to developing vaccines, rather than each vaccine manufacturer collecting it individually.

- **Federally supported cGMP-compliant manufacturing facilities (applicable to preventive vaccines only)—**Vaccines must be produced in cGMP-compliant facilities before they can be administered to human patients in clinical trials. However, the number of cGMP-compliant bioproduction facilities operating in the U.S. is limited which can be disruptive to clinical development programs making them more expensive. This strategy would entail providing additional funding or other support to help increase the number/capacity of cGMP-compliant manufacturing facilities that can produce batches of vaccines for use in clinical trial studies.

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

The strategies listed above were identified via a literature review conducted during the 2016-2018 period and many overlapped with those identified in the 2014 study. Since that time, several of the strategies included herein were adopted and additional strategies have emerged, such as remote patient monitoring and virtual visits, which gained widespread adoption due to the COVID-19 pandemic. Additionally, recognizing the challenges of conducting clinical trials during a public health emergency, FDA issued a new guidance containing nonbinding recommendations on a range of issues, including the use of virtual patient visits, remote monitoring of clinical sites, and use of real-world data in 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.

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

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. Similarly, clinical trials contribute significantly to the overall cost of developing complex medical devices. One study estimates the overall cost of medical device development at $94 million (from concept to approval) for those devices that require a Premarket Application (PMA) submission with the clinical trial stage comprising 51 percent ($47.9 million) of that total (Makower, et al., 2010). Clinical trials are the principal method for collecting safety and efficacy data to inform the approval of medical products sold in the U.S, but they have become more expensive, complex, and lengthier over time. ERG's 2014 study found that the major obstacles to conducting clinical trials were high financial cost; lengthy time frames; difficulties in recruitment and retention of participants; insufficiencies in the clinical research workforce; drug sponsor-imposed barriers; regulatory and administrative barriers; the disconnect between clinical research and medical care; and barriers related to the globalization of clinical research (Eastern Research Group, Inc., 2014). The same study also examined the potential for different strategies, such as the use of electronic health records, looser trial enrollment restrictions, for alleviating these obstacles and found the use of lower-cost facilities/in-home testing and wider use of mobile technologies to be most effective in reducing costs across therapeutic areas and trial phases.

Since 2014, there have been several developments in the clinical trials and regulatory environment. These include yearly increases in FDA user fees, new FDA guidances that may

[2] We acknowledge that strategies for the identification of new compounds (e.g., high-throughput screening, in silico testing, etc.) in early drug/device 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.

increase or decrease administrative burden,[4] FDA guidances that alter trial requirements,[5] incentives in the Affordable Care Act (ACA) for the uptake and development of electronic health record systems, and the increased use of expedited programs and designations by FDA to spur medical product development, such as orphan and breakthrough therapy designations, accelerated approval based on surrogate endpoints, and use of real world evidence in regulatory decision making. Further, therapeutic targets have been evolving with an increased emphasis on rare diseases; in 2019, approximately 44 percent of novel drugs approved were orphan drugs (U.S. Food and Drug Administration, 2020a). Medical products have become increasingly complex overall, e.g., biologics, and products involving complex drug-delivery systems.

As noted in the executive summary of this report, this study was conducted before the COVID-19 pandemic and thus, does not consider its impact on the conduct of clinical trials and adaptations that were made as a result. COVID-19 has had a profound impact on the regulatory and operational aspects of the clinical trials environment. According to a 2020 study from Medidata, during the COVID-19 pandemic, about 40 percent of investigative sites transitioned to virtual patient visits, 27 percent began shipping the investigational medicinal product (IMP) direct to patients, 15 percent switched to remote lab collections, and 15 percent switched to home visits (Medidata Solutions, Inc., 2020). Recognizing the challenges of conducting clinical trials during a public health emergency, regulatory agencies around the globe, including the FDA, UK Medicines and Healthcare products Regulatory Agency (MHRA), and the European Medicines Agency (EMA), issued guidances on a range of topics, such as 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; Ochuma, 2020). The adoption of these new approaches during the pandemic has implications for the future of clinical trials. In a 2020 report, Ernst and Young found that sponsors will be looking to adopt decentralized interactions (94 percent), patient-centric workflows (76 percent), virtual environment (35 percent), refined study designs (29 percent) alternative data collection models (24 percent), therapeutic area and/or disease-specific variations (18 percent), risk-based quality processes (12 percent), and others (12 percent) in future clinical trials (Ural, 2020). While the results of this study are still relevant as some of the approaches we discuss here include those that sponsors are already looking to adopt for their future clinical trials, they need to be viewed through a different lens that is not captured as part of this report. Section 2 summarizes the different clinical trial strategies with potential to improve development efficiency identified via an environmental scan that included a review of published literature and interviews with experts. Section 3 presents our findings related to the impact of those strategies on product development cost drivers obtained from an expert opinion elicitation study. Section 4 concludes.

[4] For example, FDA published guidance in December 2012 to specifically reduce the number of uninformative individual safety reports submitted to the Agency (U.S. Food and Drug Administration, 2012b).

[5] For example, FDA issued a draft guidance entitled Demonstrating Substantial Evidence of Effectiveness for Human Drug and Biological Products in December 2019 which provides examples of "circumstances where additional flexibility may be warranted," in the level of quality and quantity of clinical evidence needed to support effectiveness (U.S. Food and Drug Administration, 2019b).

2 PROMISING CLINICAL STRATEGIES WITH POTENTIAL TO IMPROVE DEVELOPMENT EFFICIENCY

We reviewed the literature and conducted interviews with clinical trial experts to identify promising clinical strategies with potential to reduce time and cost of conducting drug, preventive vaccine, and therapeutic complex medical device clinical trials. As noted earlier, we had previously conducted a study under contract to ASPE that looked at the costs and barriers associated with clinical trials and identified possible strategies that would improve the efficiency of clinical trials by mitigating or eliminating those barriers (Eastern Research Group, Inc., 2014). The review we undertook built on that previous work by identifying new strategies and new data to model the impact of those strategies on development costs.

Our literature search targeted several categories of literature: peer-reviewed articles in scientific journals, unpublished papers and presentations, white papers, gray literature, and news stories and occasional pieces appearing in newspapers and magazines or other print media outlets. Our search methodology featured systematic inquiries of PubMed, ScienceDirect, and Google Scholar. We used search terms in various combinations using logic strings, such as "[drug development* OR vaccine* OR medical device*] AND cost*," "[drug* OR vaccine* OR medical device*] AND clinical trials," "[drug OR vaccine OR medical device] development pathway*," etc. to query each source.

We also reviewed relevant government publications, presentations, and datasets, including FDA Prescription Drug User Fee Act (PDUFA) and Medical Device User Fee Amendments (MDUFA) performance reports, FDA presentations, guidance documents, and other white papers. Where an article was particularly useful, we also employed a "snowball" type search strategy and reviewed the sources cited as well as sources citing that article.

The aim of the literature review was to identify the most promising innovations and methods for clinical research, such as use of mobile technologies, that have the potential to reduce drug development costs. The search focused on literature that has been published since we completed the prior round of data gathering in approximately 2012 for the previous study and covered the period from 2012 through 2017. In some cases, however, we included particularly useful articles that were cited in the previous 2014 study or that were published before 2012.

To supplement the literature review and to provide further context for our findings, we also interviewed several experts in drug, vaccine, and medical device development including academic researchers, developers, clinical trial monitors at contract research organizations, and industry trade associations. The interviews were semi-structured in nature and probed the interviewee for information on the potential impact the identified clinical trial strategies could be expected to have on development costs. For each interview, our questions were limited to those strategies with which the interviewee had applied expertise in (e.g., use of registry data, standardized contracts).

Based on our literature review and discussions with experts, we identified a total of 35 strategies that fall into 15 aggregate categories as shown in Table 1. We found studies that provided "quantitative information that can be used to estimate the potential impacts for 11 of the 35 strategies (Table 2). The strategies with the biggest data gaps were FDA-focused, or associated with improving public understanding of clinical trials, workforce training, and clinical trial networks.

We discuss each of the strategies depicted in Table 1 in further detail in the following sections. As information on clinical trials for drugs was most abundant in the literature, the strategy summaries below primarily contain information on clinical trials for drugs. Wherever possible, information specific to preventive vaccine or therapeutic complex medical device trials is identified explicitly. To help address this imbalance, the expert elicitation described in Section 3 covered all three types of medical products.

Table 1. Strategy Overview

Strategy	Quantitative Information? [a]
2.1. Technology-Intensive Approaches	
2.1.1. Infrastructure for Online Trial Management	
2.1.2. Wider Use of Mobile Technologies, Including Electronic Data Capture (EDC)	✓
2.2. Simplify Clinical Trial Protocols (Data Collection and Verification) and Reduce Amendments	
2.2.1. Simplified Clinical Trial Protocols and Reduced Amendments	✓
2.2.2. Reduced Source Data Verification (SDV)	✓
2.3. Use of Lower-Cost Facilities or At-Home Testing	
2.4. Improve FDA Review Process, Regulations, and Guidance	
2.4.1. Work to Improve Consistency in Guidance, Regulations, and Interpretation Among FDA, the National Institutes of Health (NIH), the NIH Office of Clinical Research (OCR), and HHS' Office for Human Research Protections (OHRP)	
2.4.2. Fill in Gaps where Guidance is Lacking and Improve Clarity of Existing Guidance	
2.4.3. Improve the Predictability of the Review Process by Setting Firm Targets and Commitments	✓
2.4.4. Engage in More Frequent and Timely Interactions with Industry	✓
2.4.5. Temporarily Alter Regulatory Requirements to Permit Pilot Studies of Clinical Trial Approaches	
2.4.6. Allow Fewer Exposures for Long-term Toxicity Studies	
2.4.7. Staged Approval Process	✓
2.5. Biomarkers as Surrogate Endpoints	✓
2.6. Improve Patient, Physician, and Public Understanding of Clinical Trials and the Value of Participation	
2.6.1. Clinicaltrials.gov Improvements	
2.6.2. Engage Patients in the Process of Identifying Research Questions	
2.6.3. Use Social Media for Patient Outreach	
2.6.4. Periodic Physician Updates	
2.6.5. Patient Education and/or Campaign to Build Public Support for Clinical Research	
2.7. Clinical Research Workforce and Training	
2.7.1. Develop Investigator Training Infrastructure and Materials	
2.7.2. Promote Expansion of the Clinical Research-capable Workforce	
2.8. Real-World Data	
2.8.1. Use of Electronic Health Records	✓
2.8.2. Encourage Use of Pragmatic or Practical Clinical Trials (PCTs)	
2.8.3. Use Registry Data	✓

Strategy	Quantitative Information? [a]
2.8.4. Utilize "Big Data" Approaches	
2.8.5. Looser Trial Enrollment Restrictions	
2.8.6. Encourage Sponsors to Integrate Study Designs with Clinical Practice Flows and Engage Site Investigators in the Study Design Process	
2.9. Encourage Adaptive Design	✓
2.10. Standardized Contracts	✓
2.11. Clinical Trial Networks	
2.11.1. Engage Regulatory Bodies, Industry, Researchers, and Others in Collaborative Initiatives	
2.11.2. Develop and Support Permanent Networks of Resources that will Provide Consistent Trial Infrastructure	
2.12. Centralized Institutional Review Boards (IRBs)	
2.13. CDC/NIH Collection of Epidemiological Data	
2.14. Support for cGMP-Compliant Manufacturing Facilities	

[a] Indicates that there are one or more published studies that provide quantified estimates of time and/or cost savings associated with the strategy. See Table 2 for more detail on the actionable findings identified.

Table 2. Quantitative Information Available by Strategy in the Literature

Strategy	Parameter	Quantitative Findings from Literature
2.1.2. Wider Use of Mobile Technologies, Including Electronic Data Capture (EDC)	Cost	▪ ***Eisenstein et al.*** (2008): "We assessed the influence of EDC versus a paper case report form (CRF) upon total trial costs and found that the use of EDC reduced total trial costs in our pharmaceutical industry trial simulations by 9.8 percent (18.8 percent after excluding site payments)."
	Duration	▪ ***Eisenstein et al.*** (2008): "Two-month reduction in study close out time, as well as by the elimination of query processing, data entry, and medical coding at the coordinating center." ▪ ***Staziaki et al.*** (2016): "Mean time to collect data using EDC in minutes was 6.2 ± 2.3, whereas using a spreadsheet was 8.0 ± 2.0 (P <.001), resulting in a reduction of 1.8 out of 8 minutes (22 percent)."
2.2.1. Simplified Clinical Trial Protocols and Reduced Amendments	Cost	▪ ***Getz*** (2014) ***& Getz et al.*** (2011)***:*** "40 percent of protocols were amended prior to the first subject/first visit" and 37 percent were avoidable. ▪ ***Getz et al.*** (2013) ***& Getz et al.*** (2011)***:*** Each amendment costs $453,932 (in 2011 $).
	Duration	▪ ***Getz et al.*** (2013) ***& Getz et al.*** (2011)***:*** Each amendment takes one to four months to implement.
2.2.2. Reduced Source Data Verification (SDV)	Cost	▪ ***Shore et al.*** (2012) ***& Eisenstein et al.*** (2008): Model-based estimate: Switch from 100 percent on-site data verification to centralized monitoring reduced site visits from 24 to four and was "associated with an overall reduction of total trial costs of 21 percent." ▪ ***Funning et al.*** (2009): On-site monitoring for SDV accounts for up to 25 percent of the total clinical trial cost. ▪ ***Uren et al.*** (2013): Monitoring adds 25 percent to 35 percent to typical Phase 3 trial costs, but "reducing monitoring by half would be quite feasible without compromising the overall quality of the data."
	Duration	▪ ***Bakobaki et al.*** (2012): 31 person days to conduct four site visits.
2.4.3. Improve the Predictability of the Review Process by Setting Firm Targets and Commitments	Duration	▪ ***ERG*** (2016): As expected, compared to PDUFA IV, time from application receipt to first-cycle action under PDUFA V increased by approximately 2 months for approvals, 2 months for complete responses, and 2.3 months for withdrawals.
	Phase Transition Success Probability	▪ ***ERG*** (2016): Under PDUFA V, FDA increased first-cycle approval rate compared to PDUFA IV by 24.7 percentage points (overall), 18.3 percentage points (priority review), and 24.6 percentage points (standard review).
2.4.4. Engage in More Frequent and Timely Interactions with Industry	Phase Transition Success Probability	▪ ***FDA*** (2006a)***:*** End-of-Phase 2 meetings between FDA and industry lead to higher first-cycle approval rates (52 percent for products with those meetings vs. 29 percent for those without).

Strategy	Parameter	Quantitative Findings from Literature
2.4.7. Staged Approval Process	Cost	▪ ***Kocher & Roberts*** (2014): "We estimate that development costs for drugs could be reduced by as much as 90 percent…if the threshold for initial approval were defined in terms of efficacy and fundamental safety."
	Duration	▪ ***Kocher & Roberts*** (2014): "We estimate that…the time required [could be reduced by as much as] 50 percent, if the threshold for initial approval were defined in terms of efficacy and fundamental safety."
2.5. Biomarkers as Surrogate Endpoints	Cost	▪ ***Miyamoto & Kakkis*** (2011): A simulated comparison of "clinical- or surrogate-based clinical development programs…showed that the use of the AA [Accelerated Approval] pathway led to a decrease in cost to approval of 62 percent and an increase in net present value (NPV) from a mean of $23 M to $72."
	Duration	▪ ***Krishna et al.*** (2008): During the development of sitagliptin for type 2 diabetes, biomarker use "facilitated [the] design of clinical efficacy trials" and "streamlin[ed] dose focus and optimization, the net impact of which reduced overall cycle time to filing [by 1.4 years] compared to the industry average."
2.8.1. Use of Electronic Health Records	Cost	▪ ***Beresniak et al.*** (2016)***:*** Implementing the European Electronic Health Records for Clinical Research (EHR4CR) platform is expected to reduce protocol feasibility assessment costs by 50 percent, patient identification for research costs by 53 percent, and clinical study execution costs by 48 percent. ▪ ***Uren et al.*** (2013): EHRs enable remote, web-based SDV which could reduce monitoring expenditures by up to 50 percent (based on a Phase 3 oncology trial in which 4 out of 6 monitoring visits were performed remotely). ▪ ***Uren et al.*** (2013): Travel costs during the [web-based SDV] feasibility study was reduced from $3,000 to $1,000 (based on a Phase 3 oncology trial in which 4 out of 6 monitoring visits were performed remotely). ▪ ***Christel*** (2015): Using algorithms to filter EHRs for exclusion/inclusion criteria "such as previous clinics visited, ICD-9 codes, medications, or common demographic elements" can reduce research coordinator workload by 95 percent to 99 percent.
2.8.3. Use Registry Data	Cost	▪ ***James et al.*** (2015): The Thrombus Aspiration in ST-Elevation Myocardial Infarction in Scandinavia (TASTE) trial cost "~$400,000, compared with tens of millions of dollars for a study of equivalent size using a traditional industry-funded trial model" (note: performed using a registry platform with existing high-quality, validated EHR data). ▪ ***Li et al.*** (2016)***, James et al.*** (2015)***, & Frobert et al.*** (2013): Per patient costs in the TASTE trial ($50) were an estimated 90 to 98 percent cheaper than a conventional randomized control trial.

Strategy	Parameter	Quantitative Findings from Literature
		▪ ***Li et al.*** (2016)***, Huang et al.*** (2013)***, Goeree et al.*** (2013)***, & Kaczoroski et al.*** (2011): Low per patient costs—$16 and $40—were also reported in the REDUCE MRSA and CHAP trials, respectively.
2.9. Encourage Adaptive Design	Cost	▪ ***David et al.*** (2015): When compared to a conventional design, models indicate that seamless Phase 2-3I studies with one interim analysis (with the goal to maximize value) could lead to a 14 percent reduction in sample size…a 729 percent increase in ENPV; a 170 percent increase in cost to the first opportunity for clinical data-based decision-making. ▪ ***David et al.*** (2015): When compared to a conventional design, models indicate that seamless Phase 2-3 studies with two interim analyses (with the goal to shorten the time to the first opportunity to make clinical data-based decisions) could lead to a 31 percent reduction in sample size…a 584 percent increase in ENPV…a 15 percent increase in cost to the first opportunity for clinical data-based decision-making. ▪ ***Senchaudhuri*** (2015): "Employing an [inferentially] seamless adaptive late phase trial reduced sample size from 520 to 350." ▪ ***U.S. Food and Drug Administration*** (2019c): "In a Phase 3 trial that compared the angiotensin receptor–neprilysin inhibitor LCZ696 with enalapril in patients who had heart failure, "the addition of interim analyses with stopping rules for efficacy reduced the expected sample size and expected duration of the trial while maintaining a similar probability of trial success, relative to a trial with a single analysis after observation of a fixed total number of events."
	Duration	▪ ***Cuffe et al.*** (2014): "It was estimated that, compared with a conventional separate and sequential Phase 2 and Phase 3 programme, cediranib could be made available to patients 1–2 years sooner [using seamless Phase 2-3 trial]." ▪ ***Senchaudhuri*** (2015): "When conducting early phase trials, seamless proof-of-concept and dose-finding trials have also become more popular…Cytel Consultants recently reduced trial time by an expected 9-12 months (and 100 fewer patients) by employing such a design." ▪ ***David et al.*** (2015): When compared to a conventional design, models indicate that seamless Phase 2-3 studies with one interim analysis (with the goal to maximize value) could lead to a…42 percent decrease in time to market…a 14 percent reduction in time to the first opportunity for clinical data-based decision-making. ▪ ***David et al.*** (2015): When compared to a conventional design, models indicate that seamless Phase 2-3 studies with two interim analyses (with the goal to shorten the time to the first opportunity to make clinical data-based decisions) could lead to a…44 percent decrease in time to market…a 53 percent reduction in time to the first opportunity for clinical data-based decision-making.

Strategy	Parameter	Quantitative Findings from Literature
		▪ ***U.S. Food and Drug Administration*** (2019c): "In a Phase 3 trial that compared the angiotensin receptor–neprilysin inhibitor LCZ696 with enalapril in patients who had heart failure, "the addition of interim analyses with stopping rules for efficacy reduced the expected sample size and expected duration of the trial while maintaining a similar probability of trial success, relative to a trial with a single analysis after observation of a fixed total number of events."
	Phase Transition Success Probability	▪ ***David et al.*** (2015): When compared to a conventional design, models indicate that seamless Phase 2-3 studies with one interim analysis (with the goal to maximize value) could lead to a…27 percent increase in probability of success.
2.10. Standardized Contracts	Duration	▪ ***Kiriakis et al.*** (2013): 2010 Clinical and Translational Science Awards (CTSA) sites contracts processing study: Use of master agreements and previously negotiated terms were associated with significant reduction of final contract negotiation times by a mean of 33 days and 22 days, respectively. ▪ ***Christel*** (2015)***:*** Program that included issuing no-negotiated contracts (as well as other interventions) enrolled patients 100 percent faster.

2.1 TECHNOLOGY-INTENSIVE APPROACHES

2.1.1 Infrastructure for Online Trial Management

Creating infrastructure for online management of various clinical research elements can improve the uniformity and efficiency in various steps of the clinical trial process (Eisenberg, et al., 2011). Infrastructure for online trial management could include a database, website or network that matches investigators to sponsors, including information about available expertise, qualifications, capacity, resources on site, and access to various patient populations. There is also the possibility to include site performance data online. Sponsors could save time during investigator recruitment if they could use a centralized online system to 1) standardize investigator training and certification; 2) check investigators' qualifications; and 3) find qualified investigators (Eisenberg, et al., 2011). Infrastructure for online trial management could also decrease the IRB review time needed for multi-center projects; standardized digital case report forms (CRFs) could decrease the time previously required to integrate paper CRFs and/or non-standardized digital forms. An online trial management system could also improve the efficiency of conducting clinical trials by creating a space for centralized institutional review board (IRB) review for multi-center projects, notifications of adverse events and clinical trial protocol amendments, and knowledge base of standardized case report forms for data collection.

Further, the existence of an online trial management system creates the possibility for conducting web-based trials, in which patients participate at home using computers or smartphones instead of traveling to trial sites. Pfizer has attempted this "clinical trial in a box" idea, recruiting patients through internet ads and providing a website that explains the trial and allows online enrollment. All necessary materials, including the blinded study drug and a mobile app for electronic patient-reported outcomes (PROs), are sent to participants at home (Silverman, 2011).

2.1.2 Wider Use of Mobile Technologies, Including Electronic Data Capture (EDC)

Mobile technology and electronic data capture encompass a variety of strategies related to clinical trials. Both can be used to streamline patient screening and recruitment processes and allow for central statistical monitoring, minimizing direct contact with patients and the costs associated with face-to-face visits (Institute of Medicine, 2012).

In practice, using mobile technology and EDC takes many forms. This can include automated reminders for patients, automated notifications to trial staff, compliance monitoring, electronic CRF, and/or remote data collection from patients (Institute of Medicine, 2012; Cramon, et al., 2014). EDC also comprises digitizing paper forms, which has increased sites' efficiency and reduced the cost of manually entering data (Institute of Medicine, 2012). Mobile and web-based technologies have also made remote clinical trial participation possible, meaning that patients do not have to visit trial sites for investigators to record progress (Institute of Medicine, 2012; von Niederhäusern, et al., 2017).

Studies have employed EDC to capture data continuously from patients, including when they are away from the trial site. One study used EDC to more frequently assess cognitive change in individuals during home-based testing for preclinical Alzheimer's disease (Rentz, et al., 2016). In another study, assisted living residents were outfitted with body sensors that could collect "health-related vital parameters data" from them continuously (Forkan & Khalil, 2017). A third study used webcam programs to monitor sleep apnea patients (Isetta, et al., 2015).

One expert's model simulation found that the use of EDC reduced the total clinical trial costs by 9.8 percent including site payments, and 18.8 percent excluding those payments (Eisenstein, et al., 2008). The same model also reported a two-month reduction in trial close-out time related to increased efficiency from processing digital data instead of paper forms. Another expert found that collecting data with EDC instead of traditional spreadsheet software resulted in a 22 percent reduction in time spent on data collection (Staziaki, et al., 2016).

Multiple drug, preventive vaccine, and complex medical device experts agree that wider use of mobile technology and EDC would decrease clinical trial costs due to reduced onsite visits and less time spent by trial staff entering data and correcting errors. One expert noted that eliminating onsite monitoring visits could cut costs by about 30 percent. Experts had varied feedback about which trial phase(s) costs would be most impacted by the implementation of mobile technology. In early phases, investigators could use EDC to aggregate data from electronic medical records (EMRs), which reduces staff burden and decreases time spent on source data verification (SDV). A vaccine expert noted that the use of mobile technologies could have the greatest impact in Phase 1, during which assessments are the most intensive. However, three experts said that the largest financial impact would be realized in later trial phases, when investigators are potentially tracking thousands of patients for long periods of time. Less effort is required of both trial staff and patients with mobile technology's ability to passively collect data from patients, reducing the number of in-person visits. In Phase 4, digital technologies that could integrate multiple health databases to include clinical, laboratory, and specialized evaluations of patients who have received vaccines may be able to identify risks to the patient through an alert system. While employing the technology may increase costs, the resulting increase in efficiency may be more valuable.

Another benefit of increased use of mobile technologies in clinical trials is access to an expanded pool of potential patients. With fewer required in-person visits, patients from geographically remote locations may be able to participate in a trial. It is also easier to enroll and follow patients, and endpoints would be captured and evaluated in a shorter timeframe. With respect to the increasing trend of conducting clinical trials overseas, the prevalence of cell phone ownership in developing countries means that the benefits of using mobile technologies in clinical studies could be realized in non-U.S.-based trials, as well.

While there remains a significant need to validate and understand how well the collected data reflects how a patient feels and functions, implementing mobile technologies such as Fitbits and electronic tablets in "take home" clinical studies can give sponsors access to real time data and facilitate the collection of patient reported outcomes (Zhang, et al., 2017;

Pan, et al., 2016). One expert noted that the ability to access more data earlier in the process helps investigators make better decisions at the stage gate level. This deeper understanding increases the chance of trial success. Investigators can use mobile technology to generate additional patient-level data, such as activity and movement. This collection of non-clinical, surrogate endpoints in Phase 2 trials can also help improve efficiency and increase likelihood of success. Multiple experts noted that electronic data capture has a higher chance of reducing cost and trial timeline as more patients are enrolled. A large, randomized dataset minimizes potential variation in data collected by different devices.

Some experts report that cost savings from mobile technologies are limited and that mobile technology-based strategies are unlikely to improve chances of trial success. The cost to distribute and manage devices is high, and additional staff and/or patient training may be required. Another expert noted that cost savings would not happen immediately, because CROs currently cannot change their pricing models, which rely on onsite visits. Moreover, less face-to-face interaction at trial sites could create an issue with patient compliance and drop-out rates. To incentivize trial participants to submit their data, investigators may consider paying participants, which increases trial costs. Multiple experts reported that increased use of mobile technologies would not improve the chance of a trial proceeding to a subsequent phase, even if data quality is improved. Mobile technologies may only be a good fit for certain therapeutic areas in which the patient is more involved in their own care.

Regulatory and timeline constraints are also potential limitations to implementing mobile technologies in clinical trials. Current FDA standards for data collection and verification in Phase 3 and 4 trials are strict but FDA is working on developing guidance for industry on the use of digital health technologies (DHTs), including mobile technologies, for approval-based indications or in the NDA/BLA phase. Further, due to the COVID-19 related public health emergency, FDA has issued new guidance containing nonbinding recommendations on a range of issues, including the use of electronic informed consent forms and use of real-world data in drug applications (U.S. Food and Drug Administration, 2021a). The use of EDC also raises questions about patient privacy and how electronic systems handle data to protect patients. Additionally, data quality and technical system discrepancies present challenges to increasing the use of mobile technology in clinical trials. Internet browser capability monitoring systems and database user access must be used and regulated to protect trial data collected electronically and ensure full system functionality. With EDC, investigators and trial staff cannot clean data at the time of entry, and methods for collecting and verifying data through digital devices and dealing with missing data must be addressed. Different wearable devices may also collect the same data in varied measurements.

2.2 SIMPLIFY CLINICAL TRIAL PROTOCOLS (DATA COLLECTION AND VERIFICATION) AND REDUCE AMENDMENTS

2.2.1 Simplified Clinical Trial Protocols and Reduced Amendments

Clinical trial protocols are "the blueprint articulating project strategy and directing project execution performed by both internal and external personnel" (Getz, 2014). Protocols sometimes require amendments after they have been approved. Amendments to protocols are "attempts to address underlying protocol design problems and external factors impacting design strategies" (Getz, 2014). These amendments sometimes require "approval from the IRB, Ethical Review Board (ERB) or regulatory authority" (Getz, 2014).

Several factors have increased the complexity of protocols and the number of amendments to protocols. The number of stakeholders influencing protocol design has increased in recent years. Stakeholders now include "scientists, regulatory agencies, health authorities, operating managers, patients/patient organizations, investigative site personnel, health care providers, policymakers and payers" (Getz, 2014). Additionally, sponsors often collect additional data "as a precautionary measure in the event that a study fails to meet its primary and key secondary objective" (Getz, 2014). Sponsors also tend to widen the scope of their protocol to ensure they collect data requested by "regulatory agencies and health authorities, purchasers and payers" (Getz, 2014).

While complex protocols collect more data, they also have drawbacks. First, they often place a higher burden on participants, thereby increasing participant withdrawals. They also create a higher burden for staff at trial sites. Complex protocols also tend to increase the costs of study monitoring, data management, and logistics. Finally, regulatory reviewers must spend more time reviewing complex protocols.

Although some protocol amendments are necessary to address protocol design problems, there are many that could have been avoided. According to one study, 57 percent of protocols had at least one substantial amendment (Korieth, 2016). An estimated 45 percent of these amendments were somewhat or completely avoidable (Korieth, 2016). The largest costs associated with amendments are IRB fees and change orders to vendor contracts. The median direct cost to implement a substantial Phase 2 amendment was $141,000, while the median cost to implement a Phase 3 amendment was $535,000 (Korieth, 2016). Implementing an amendment can also add up to 6 months to study cycle times (Korieth, 2016).

This strategy aims to simplify data collection and verification protocols and reduce avoidable protocol amendments. It encourages sponsors to simplify clinical trial protocols, where possible, and ensure that sponsors have a clear understanding of what is required by FDA and what is superfluous.

Experts agree that simplifying data collection and verification protocols would help reduce costs. One expert indicated that the greatest savings would result from reducing recruitment time, monitoring costs, and site costs. Multiple experts indicated that greatest cost

savings would occur during Phase 2 and Phase 3. A vaccine expert also suggested that simplifying protocols would reduce costs during the FDA approval phase.

There were two initiatives to simplify protocols. The "Standard Protocol Items: Recommendations for Interventional Trials" (SPIRIT) Statement is one existing approach to standardize protocols. SPIRIT provides an evidence-based set of protocols available for free (SPIRIT Statement, 2017a; SPIRIT Statement, 2017b; Getz, 2014). Similarly, TransCelerate Biopharma Inc. has developed a "Common Protocol Template" (CPT) with a model structure and template language that aligns with the NIH/FDA-developed template. CPT was finalized in 2017 (TransCelerate BioPharma Inc, 2016a; Fassbender, 2017).

Experts also agree that reducing avoidable amendments would help reduce costs. One expert indicated that the amendment process can lead to very substantial delays, and that the ability to accommodate emerging data could decrease trial time significantly. A vaccine expert noted that reducing amendments helps reduce the turn-around time for FDA's review, comments, and approval. Another vaccine expert indicated that cost savings would be greatest in studies carried out across multiple sites.

Several experts indicated that, while simplifying data collection could greatly reduce costs, it may not lead to substantial time savings. Experts also suggested that simplifying protocols would not yield cost savings during Phase 1 due to challenges in recruiting and the diversity of candidates.

One challenge to simplifying clinical trial protocols is that sponsors may set up their protocols to collect data not directly related to achieving FDA approval. For example, sponsors might "piggyback" on a study to gather data for other ongoing research projects or tack on supplemental data collections to be used when submitting drug applications to foreign health authorities. Further complicating attempts to simplify protocols is that sponsors might retain measures or endpoints that become obsolete, even after these measures and endpoints have been updated or replaced. Sponsors collect these "extra" data in case the FDA reviewer requests it later in the process. Experts noted that sponsors could reduce time spent collecting data if FDA communicated more clearly about its expected data requirements.

2.2.2 Reduced Source Data Verification (SDV)

Source data verification (SDV) is "the process of ensuring that the data reported for analyses accurately reflect the source data at the clinical trial site." Source data includes "original records documenting clinical findings, observations, and any other activities" (Sheetz, et al., 2014). Sponsors often rely on source data verification (SDV) to ensure data quality (Sheetz, et al., 2014; Houston, et al., 2018; Agrafiotis, et al., 2018). The frequency of SDV varies by trial, "from every week up to once every 3 years" (Macefield, et al., 2013).

Historically, sponsors have conducted SDV for 100 percent of site data (Sheetz, et al., 2014; van den Bor, et al., 2016). However, "SDV of 100 percent of the data does not guarantee error-free results" (Sheetz, et al., 2014). Additionally, most of the errors found through SDV do

not directly impact the results or interpretation of trials (Sheetz, et al., 2014; Bakobaki, et al., 2012). This is because most SDV findings are trivial errors in patient biographical data, not safety or efficacy data associated with clinical endpoints.

Due to these drawbacks, FDA has sought alternatives to conducting SDV for 100 percent of site data. In 2013, FDA issued guidance that encourages study sponsors to implement centralized monitoring in lieu of 100 percent site visits.[6] However, one 2014 study found that sponsors still conducted 100 percent SDV (Getz, 2014). A 2015 study was also unable to determine whether trial sponsors used centralized monitoring (Vose, et al., 2016).

This strategy aims to engage sponsors in discussions on the topic of data and site monitoring to ensure that they are aware of FDA guidance stating that 100 percent source data verification is not required.

Experts agreed that SDV costs are significant and that reducing the burden of SDV would help reduce costs. Additionally, they argued that reducing SDV is not expected to impair data quality or study outcomes, as the few errors that SDV discovers are typically confined to patient biographical data.

Experts provided a range of estimates for time and money spent on SDV. According to one expert, about 35 to 40 percent of a large cardiovascular trial's costs are driven by site management or on-site monitoring. Another expert indicated that monitoring accounts for about 15 to 17 percent of a study budget, and that reducing these practices would create cost savings of 5 to 10 percent. Another expert noted that SDV makes up 50 to 75 percent of the time and 25 to 90 percent of the costs for clinical trials.

Several studies have also addressed the costs and time associated with SDV. Two studies reported that on-site monitoring for SDV accounts for 15 to 25 percent of total clinical trial costs (Funning, et al., 2009; Hughes, 2017). For one Phase 3 study, monitoring increased trial costs by 25 to 35 percent (Uren, et al., 2013). A model-based estimate found that switching from 100 percent on-site data verification to centralized monitoring reduced total trial costs by 21 percent and reduced site visits from 24 to 4 (Shore, et al., 2012; Eisenstein, et al., 2008). Another study also found that 4 site visits required a total of 31 person-days of work (Bakobaki, et al., 2012).

Several experts noted that SDV costs are proportional to the number of patients included in a study. As a result, the largest savings would occur during later trial phases, when larger numbers of patients impose greater burdens on monitors and study coordinators. One expert also indicated that reducing SDV is most applicable to large trials with a low number of minor adverse events, as these trials have greater financial incentives and lower risks. Reduced

[6] FDA defines centralized monitoring as "…a remote evaluation carried out by sponsor personnel or representatives (e.g., clinical monitors, data management personnel, or statisticians) at a location other than the sites at which the clinical investigation is being conducted" (U.S. Food and Drug Administration, 2013). Centralized monitoring relies on a statistical approach to handle the clinical trial information collected/submitted from different sites and patients for a study (Malia, 2019).

SDV is not advised for higher-risk, small population studies, which require careful adjudication of endpoints and can lead to serious adverse events. Experts also suggested that SDV will become less relevant as electronic medical record systems, which allow remote monitoring, become more common.

Many experts noted that, while reducing SDV might reduce costs, it will not necessarily save time. Moreover, they noted that reducing SDV would have a negligible effect on costs during early trial phases. Several experts also indicated that they still practice 100 percent SDV to avoid penalties from FDA due to data errors. They suggested that FDA reviewers should be more willing to accept withdrawals, missing data, and trivial errors.

One expert indicated that the degree of necessary SDV depends on the type of trial. For example, small trials with a high number of severe adverse events (such as oncology) should continue to require 100 percent SDV. And some experts indicated that, while time-consuming, SDV does provide benefits. These benefits include identifying data errors and allowing on-site monitors to perform education at sites with high turnover. Finally, one expert suggested that replacing SDV with risk-based monitoring would yield better results than merely reducing SDV.

2.3 USE OF LOWER-COST FACILITIES OR AT-HOME TESTING

This strategy encourages sponsors to utilize lower-cost facilities, such as local clinics and pharmacies, for data collection whenever possible to reduce the need for costly infrastructure and overhead. They can also conduct follow-up visits beyond the initial trial period at local centers to minimize travel and time costs for participants and thereby possibly improve retention. At-home testing is facilitated by and may depend on the use of mobile technologies and EDC.

Examples of this strategy include sending a mobile phlebotomist to patients' homes and having patients go to storefront laboratories to get their blood drawn, rather than at an investigative site (Christel, 2015). In addition, at-home blood pressure measurement for anti-hypertensive drugs can lower costs while increasing the number of measurements and identify changes in blood pressure with greater precision (Stergiou & Ntineri, 2016).

The main benefits of employing lower cost facilities or at-home testing are facility, staff, and equipment cost savings and reduced burden for trial participants. Because many patients do not live near academic research centers, at-home testing allows for patients from an expanded area to participate in trials. The use of local facilities and/or at-home testing also allows for more frequent assessments and may reduce patient dropout rates.

While a sponsor may save money on facility, equipment, and staff costs, sponsors or investigators may need to provide support, training, and/or funding to help patients' local physicians participate in the trials if they are not being conducted at academic research centers. There also are several disadvantages, especially for Phase 2 and 3 studies, as the risk of Type II errors might increase due to noise from the use of multiple assays and/or decrease in the quality of data collected.

2.4 IMPROVE FDA REVIEW PROCESS, REGULATIONS, AND GUIDANCE

Given the paucity of literature related to this area as noted above, most of the discussion below is based on experts interviewed for the study. The expert opinions presented do not account for the additional resource burden associated with implementation of these strategies. While these areas are regularly addressed in user fee act negotiations between industry and FDA, which in turn determine agreed upon review clocks and types of communications, there appears to be a continuous desire to improve these aspects. Thus, the strategies described below should be viewed through that lens.

2.4.1 Work to Improve Consistency in Guidance, Regulations, and Interpretation Among FDA, the National Institutes of Health (NIH), the NIH Office of Clinical Research (OCR), and HHS' Office for Human Research Protections (OHRP)

Efforts have been made to modernize the way regulations, policies, and practices related to the way clinical trials are conducted. Because clinical trials are a critical source of evidence to inform medical policy and practice, improved consistency among FDA, NIH, NIH's Office of Clinical Research (OCR), and HHS's Office for Human Research Protections (OHRP) could ease the conduct of clinical trials.

In the past, areas for interagency harmonization have included conflict of interest disclosures, adverse event reporting, privacy requirements, and central IRBs (U.S. Food and Drug Administration, 2012a). Experts agree that HHS leadership encourages strategy changes that would increase fluidity and consistency in guidance and procedures between and within agencies. The primary challenge to improved consistency in guidance, regulations, and interpretation among HHS agencies is that such consistency is still a challenge *within* agencies. Multiple experts agreed that there is a disconnect between the policy and reviewer levels at FDA, suggesting that consistent interpretation of guidance within FDA is a first step before there is interagency harmonization. Even if education and training are prioritized to promote intra-agency consistency, the way individual reviewers interpret guidance could present a persistent problem.

According to one expert, for example, despite FDA guidance permitting reduced source data verification and risk-based monitoring, individual reviewers may require evidence of traditional data monitoring. A potential solution to improve consistency and overall efficiency would be to mandate education and training when new policies and guidance documents are promulgated for all levels of FDA staff One expert remarked that policy at upper levels of FDA may already be successfully implemented, but more work is needed to implement those strategies at the reviewer level. The same expert also noted that coordination and communication among the three centers within FDA: Center for Devices and Radiological Health (CDRH), Center for Biologics Evaluation and Research (CBER), and Center for Drug Evaluation and Research (CDER) could be improved.

Additionally, one expert noted that measuring tools for some conditions (such as migraines and Alzheimer's)—even if validated by academia and industry—might be accepted by

some FDA centers, but not others.[7] The lack of a streamlined process for validating measuring tools across CDRH, CDER, and CBER can add to the time and cost of clinical trials if the same measuring tool must be re-validated in multiple settings.

Various options for improving consistency in guidance, regulations, and policy interpretations among agencies are already underway. For example, agencies have discussed implementing a web-based federal-wide portal that would allow investigators to submit certain pre- and post-market safety data electronically and deliver it automatically to appropriate agencies and oversight bodies. The FDA, together with the NIH, developed a pilot portal to explore this possibility (U.S. Food and Drug Administration, 2012a). Following the development of that pilot portal, several similar initiatives and pilot programs have been brought into existence. In additional to the pilot portal, the FDA is also working with the Clinical Data Interchange of Standards Consortium (CDISC) and the research community to develop standard terminology for case report forms (U.S. Food and Drug Administration, 2012a). The use of consistent terminology and data fields could help facilitate information sharing and coordination among agencies involved with clinical research.

2.4.2 Fill in Gaps where Guidance is Lacking and Improve Clarity of Existing Guidance

Although guidance documents represent FDA's nonbinding, "current thinking" on particular topics, they are nonetheless interpreted by industry as granting "regulatory endorsement" to the topics they cover (Forda, et al., 2013). As such, filling in the gaps in existing guidance would likely improve industry's comfort level with implementing cost- and time-saving approaches outlined in FDA guidance documents.[8] For example, one expert noted that risk-based monitoring (RBM) has great potential for reducing trial costs and timelines (Agrafiotis, et al., 2018), but that industry is still unclear about which clinical data are considered critical and are therefore reluctant to implement RBM approaches. This expert suggested that FDA should allocate more resources to helping industry understand FDA's RBM and eSource guidance.

Areas where guidance is perceived as lacking by some experts include very rare diseases, areas of unmet need (e.g., anti-infectives and obesity), and personalized medicine (Forda, et al., 2013). Additionally, uncertainty around terms *such as* "unmet need" and "major therapeutic advantage" can hinder industry's ability to take advantage of expedited development pathways.

Clearer communication of expectations related to regulations and guidance would also help inform industry decision-making. Some experts describe the language used in regulations and guidance as vague and open-ended. In some cases, vague language is used to provide

[7] Depending on the context of use for the tool, validation requirements may be different. This is a potential complicating factor in validating a tool across CDRH, CDER and CBER. Further, there are ongoing efforts at FDA, such as the Drug Development Tool Qualification process under the 21st Century Cures Act, regarding this issue (U.S. Food and Drug Administration, 2021c).

[8] On the other hand, because guidances are technically non-binding but often closely followed by sponsors, being less-specific may allow sponsors the flexibility to proceed as they see fit within a set of guidelines.

flexibility for clinical trials. In other cases, however, vague language is unintentional or unnecessary. In these instances, vague guidance should be replaced with robust and specific language to improve the clarity of guidance. To do this, the FDA has considered soliciting input from sponsors on problematic passages to determine the optimal level of specificity in each case.

If clarity of existing guidance documents were improved and gaps where guidance documents are missing were filled in, it would increase the likelihood that industry would take advantage of efficiency-improving approaches already endorsed by FDA and novel approaches that are in the pipeline.

Few challenges or drawbacks exist from filling in the gaps and solidifying existing guidance documents. Experts mentioned that publishing more guidance documents will impact some development programs more than others.

2.4.3 Improve the Predictability of the Review Process by Setting Firm Targets and Commitments

Since passage of the Prescription Drug User Fee Act (PDUFA) in 1992, FDA has been reviewing and taking action on New Drug Applications (NDAs) and Biologics License Applications (BLAs) in more predictable timeframes (Eastern Research Group, Inc., 2016). The fifth authorization of PDUFA seeks to promote enhanced communication and predictability between the FDA and applicants (Eastern Research Group, Inc., 2016). These discussions have continued through PDUFA VI (U.S. Food and Drug Administration, 2016b) and are also part of the initial discussions of PDUFA VII (Terry, 2020; PhRMA, 2021).

A study conducted by ERG (2016) found several benefits under PDUFA V related to improving predictability of the review process. Regardless of whether their applications were approved, applicants found the transparency, efficiency, and predictability of the program valuable. Clear program milestone communications, such as mid-cycle communications and late-cycle meetings in which targets and commitments are communicated can enhance the predictability of reviews (Ewart, et al., 2018). These meetings can serve as “anchor points” for applicants and FDA, providing a forum for holistic, multi-disciplinary discussion of application status and paths forward. Such discussions in which targets and goals are relayed are also the time to resolve approvability issues. ERG’s (2016) study found that providing target dates for responses gave applicants and reviewers a timeline to work with in light of a high volume of information requests. Other small steps to improve communication and predictability can have an outside impact. For example, applicants remarked that they would benefit from receiving a confirmation during the review process that their responses were complete (Eastern Research Group, Inc., 2016). Adding this step to the review process improves predictability for both applicants and reviewers.

Inconsistent availability and communication of information regarding the status and results of pre-approval inspections hinders predictability of the review process both internally and between FDA and applicants (Eastern Research Group, Inc., 2016).

FDA expectations, requirements, and review play a significant role in influencing the amount of money and time spent by sponsors before and during clinical trials. This strategy would entail creating more opportunities to identify, discuss, and resolve substantial issues during FDA review, continuing to educate FDA reviewers on changes in FDA policy, and providing more transparency to sponsors about which endpoints are required. In general, FDA input is regarded as highly valuable by sponsors and this strategy centers on creating more opportunities for FDA interactions and buy-in.

One drug expert noted that CDER and CBER diverge in their approaches to prophylactic biologics, which creates inconsistency in response and overlap in responsibilities. Continued internal review at FDA could further analyze how long it takes to provide feedback to sponsors, measure ease of communication between sponsors and reviewers, and identify differences in the concentration of responsibilities that could be inhibiting the clinical trials review process.

Another proposed method to increase the efficiency of FDA's review process is to implement a standardized training program for new reviewers and develop methods to ensure updates to policies and practices are communicated to experienced reviewers. Two possible methods for long-term training include training refreshers and mandatory certifications. A standardized training program would aim to not only increase consistency but also increase review quality. One drug expert noted that much of the high-cost, low-value administrative work during clinical trials is driven by fear of negative FDA feedback. A complex medical device expert said that the lack of a truly interactive review process with FDA creates confusion and extends the review process. CDRH has implemented a new reviewer training through its Reviewer Certification Program (RCP). The RCP provides core reviewer skills and competencies and according to an evaluation study conducted in 2018 has had "…a positive impact on providing reviewers with the foundation and skills necessary to perform efficient submission reviews" (Booz Allen Hamilton, 2018).

Ambiguity from the FDA on which methods are acceptable for RBM adoption and its effect on the review process is also an issue. With rapidly changing technology, FDA could reconsider which data and methods are acceptable for trials to ease the cost burden. On the other hand, some experts do not think any improvements in FDA review process efficiency are needed. One drug expert commented that FDA is not the cause of inefficient clinical trials, and a complex medical device expert added that companies underuse the pre-submission process and conduct unnecessary tests before contacting FDA to figure out what is required. Another drug expert noted that the Fast Track designation has made the review process and interactions between sponsors and the FDA more efficient.

Experts' input varied about the potential benefits of FDA improving its review process. Given the impact and influence of FDA expectations on trial structure and operations, numerous experts stated that improvements in the review process had the potential to reduce trial cost, reduce trial duration, and increase the probability of phase transition success. Regarding cost, one drug expert estimated that allowing RBM could decrease trial costs by about 20 or 30 percent if optimally adopted. One drug expert noted that improved

transparency from FDA about expected endpoints could impact the design and duration of a trial's later phases, which would increase the development program's probability of a success. Increased communication during protocol development could also streamline the trial process and decrease the time needed to start a trial.

Both drug and vaccine experts indicated that improved communication with FDA would positively impact development programs across multiple phases. During the preclinical stage and Phase 1, interactions with FDA could confirm clinical endpoints and medical need for the program and establish a preliminary outline for the clinical development plan. In Phase 2 vaccine trials, improved timeliness of communication with FDA increases the likelihood that trials achieve proof of concept, dose optimization, and entry into target populations, which is especially important for pediatric studies with concomitant vaccinations. During the transition from Phase 2 to Phase 3, development programs with FDA buy-in can proceed with better endorsement of objectives and statistical analyses, and feedback from inspections during Phase 2 studies might decrease the risk of bioresearch monitoring findings later in the development process.

There are no challenges associated with this strategy other than the resource constraints faced by FDA, though several experts questioned whether improvements in FDA review process efficiency would substantially impact trial cost or duration. Two drug experts who thought a trial's chance of success may increase with more FDA interaction and guidance on data requirements, they did not think these would have a material impact on trial time or cost.

2.4.4 Engage in More Frequent and Timely Interactions with Industry

By engaging in more frequent and timely interactions with industry, FDA can improve the efficiency of their review process and help sponsors make more informed development decisions (Cecchini, et al., 2019). For example, FDA could let sponsors know about potential issues as soon as they come up rather than waiting to communicate at a later point in time.

End-of-Phase 2 meetings between FDA and industry led to higher first-cycle approval rates of products undergoing clinical trials. Approval rates were 52 percent for products that had these meetings and 29 percent for those that did not have the meetings (U.S. Food and Drug Administration, 2006a).

One expert noted that more frequent interactions would reduce costs, increase probability of trial success, and reduce review time because the FDA could inform drug companies what they need to do to enhance their data collection process. Similarly, another expert believes that the drug industry would benefit if the FDA was more transparent in communicating their desired outcomes and standards.

There are many other benefits to more frequent and timely interactions beyond those that sponsors can already request between FDA and industry. FDA reviewers agree that starting and maintaining conversations early with sponsors is the most important factor in

identifying problems and providing solutions in a timely manner (U.S. Food and Drug Administration, 2006a). Early and frequent dialogue between industry and FDA can also help ensure that critical aspects of study design, such as selection of study populations, study end points, and drug doses, are ironed out in a timely manner (Sacks, et al., 2014). Studies show that pre-IND meetings and end of Phase 2 conferences are associated with shorter clinical development time (DiMasi & Manocchia, 1997).[9]

Some challenges exist to implementing more frequent and timely interactions between FDA and industry. Inconsistent availability and communication of information about the status of the review hinders review transparency and predictability both internally and between the FDA and applicants. In addition, increased communication between FDA and industry increases the burden on FDA's primary reviewers and regulatory project managers. This, in turn, diverts efforts away from review work because FDA representatives spend time preparing for meetings instead. Occasionally, these meetings lead to additional primary review addenda, which also increases reviewers' workload (Eastern Research Group, Inc., 2016).

2.4.5 Temporarily Alter Regulatory Requirements to Permit Pilot Studies of Clinical Trial Approaches

The idea of allowing temporary alterations to regulatory requirements to "experiment" with pilot programs was proposed at a 2012 FDA hearing on clinical trials. Such pilot programs would allow for alternative approaches to be evaluated relative to current approaches to determine whether they improve efficiency, productivity, and more (U.S. Food and Drug Administration, 2012a).

Altering regulatory requirements to allow pilot programs that explore alternative approaches to various aspects of the clinical development process has the potential to improve the efficiency of clinical trials (U.S. Food and Drug Administration, 2012a). For example, the FDA could temporarily relax their informed consent requirements to evaluate the impact of a simplified informed consent process (U.S. Food and Drug Administration, 2012a; Mahon, et al., 2015). Additionally, simplifying or altering regulatory requirements around data collection requirements could help streamline study designs (Mahon, et al., 2015).

While the FDA has expressed interest in pilot programs, a lack of consistent understanding of alternative methods and applications by reviewers could make the agency reluctant to allow temporary alterations.

[9] There are several changes FDA implemented that were not in existence when the environmental scan for this study was conducted. For example, sponsors now can voluntarily request an Initial Targeted Engagement for Regulatory Advice (INTERACT) meeting from CBER to obtain non-binding feedback on issues related to an early-stage innovative investigational product that is not yet at the pre-IND meeting phase (U.S. Food and Drug Administration, 2020c).

2.4.6 Allow Fewer Exposures for Long-term Toxicity Studies

Toxicology studies use animal testing to determine the safety of potential drugs. They "provide the supporting data to enable first-in-human (FIH) studies" (Lee-Brotherton, 2008). These supporting data include "target organs, predict toxicology, reversibility, exposure levels, [and] starting doses" (Lee-Brotherton, 2008).

Currently, all new pharmaceuticals undergo safety testing that begins "early in the exploratory development of a potential drug with acute toxicity tests" (Mestre-Ferrandiz, et al., 2012). Later, 30-day toxicity studies help "support and inform long term clinical studies, with the registration requirement of the drug in mind." Six-month animal toxicity studies continue "throughout the clinical trial process" and "data from human studies are used to inform and refine the animal studies so that they reveal more useful and accurate data" (Mestre-Ferrandiz, et al., 2012).

Toxicology studies typically require a significant amount of time and money (Van Norman, 2019). The average amount of time elapsed from the first toxicity dose to the first human dose is 9.6 months (Lee-Brotherton, 2008; Mestre-Ferrandiz, et al., 2012). Aggregate toxicology costs range from $1.5 million to $6.5 million per investigation (Stergiopoulos, et al., 2013; Mestre-Ferrandiz, et al., 2012), depending on the number of studies conducted and the animal models used. For example, a single 28-day rat study costs around $120,000, substantially less than a 28-day monkey study which costs around $555,000 (Lee-Brotherton, 2008).

While they are costly, toxicology studies do not guarantee success. The average success rate from first toxicity dose to first human dose is 70 percent (Mestre-Ferrandiz, et al., 2012) and that is only after vetting an average of 13.3 compounds to find one successful candidate for toxicity testing (Mestre-Ferrandiz, et al., 2012). Additionally, "animal models, even when they closely mirror human disease, may not afford sufficient correlation and precision to predict the human therapeutic dose" (Rosenblatt, 2017).

Preclinical data sharing could help allow fewer exposures for long-term toxicity studies. One existing program is TOX2, a preclinical safety project. Through TOX2, "12 pharmaceutical companies and several public partners have shared data from their preclinical in vivo toxicity studies, thereby creating the biggest database in this field" (Yildirim, et al., 2016). When used in combination with recent modeling and simulation approaches, TOX2 allows "better prediction of potential toxicity linked to novel compounds," which in turn permits deselecting "development compounds with a safety risk months earlier than today" (Yildirim, et al., 2016).

2.4.7 Staged Approval Process

Staged approval could entail granting provisional marketing approval to a drug, complex medical device, or preventive vaccine after safety and basic efficacy have been shown, and then continuing to collect additional safety and efficacy data. This would reduce the threshold for initial approval, perhaps with a limited patient population, and then gradually expand it as

more data are collected. This strategy revolves around striking a balance between safety, evidence development, and access to treatment (for patients) and to markets (for industry) (Woodcock, 2012).

For drug clinical trials, if the threshold for initial approval were defined "in terms of efficacy and fundamental safety," Kocher & Roberts (2014) estimate that development costs could be reduced by as much as 90 percent and trial duration reduced by as much as 50 percent.

For vaccine clinical trials, one expert estimated that if efficacy standards were loosened, there could be a 10 to 20 percent reduction in trial duration. Licensing based on immunogenicity, with data to follow, could lead to a 30 percent reduction in trial duration.

The primary benefit associated with staged approval is that less stringent efficacy requirements would lead to smaller pivotal trials with shorter enrollment periods and corresponding reductions in cost and duration. As there is higher risk tolerance for patients with unmet needs, adaptive licensing would allow promising drugs, complex medical devices, and preventive vaccines to be made available for targeted uses more quickly. Eichler et al. (2012) note that "traditional drug licensing approaches are based on binary decisions. At the moment of licensing, an experimental therapy is presumptively transformed into a fully-vetted, safe, and efficacious therapy." With staged approval, however, uncertainty is acknowledged "with iterative phases of data gathering and regulatory evaluation" (Eichler, et al., 2012).

The primary critique associated with staged approval from the perspective of clinical trial efficiency is that staged approaches may save time and money in Phase 3, but these savings are eroded by corresponding increases in complexity in Phases 2 and 4. For example, several experts indicated that, assuming the evidentiary bar for "full approval" would be unchanged from current levels, Phase 3 cost and time savings would be offset by costlier and more complex Phase 2 studies and/or the displacement of research and development time and cost onto more complex follow-on studies. Although more stringent Phase 4 commitments could potentially be offset by electronic health record (EHR) or observational data for confirmation of effect, experts agree that overall time and cost of a trial would not change because the same evidence is ultimately gathered. Experts acknowledge, however, that even if adaptive approaches do not reduce the cost burden of clinical development in aggregate, staggered costs are easier to absorb.

On the other hand, relying on follow-on studies for "full approval" introduces more opportunities for approval to be denied, thus offsetting some of the benefits of having an early revenue stream. In other words, even if limited licensing is granted more quickly, when studies are eventually conducted in larger populations, safety and efficacy issues might be exposed resulting in a decline of success rates in later stage studies. Arguing that "adaptive licensing would not address the scientific uncertainties that lead to most clinical development failures," Woodcock (2012) observes that 66 percent of studies failing in Phase 3 were terminated for lack of efficacy, "a failure of prediction that regulatory changes cannot address."

Another key challenge associated with staged approval is ensuring that there is adequate development of safety and efficacy data post-approval. Several experts noted that once a drug is approved it is "never going away" and that sponsors are less incentivized to conduct high quality RCTs. Contributing to this challenge is the prevalence of off-label drug use, which further attenuates sponsor interest in maintaining robust datasets or conducting follow-on trials post-approval. From a complex medical device perspective, one expert noted that "FDA has never withdrawn approval for a device once approved" and the expert "has no confidence that once approved, dangerous devices will be removed from the market."

2.5 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 among academics, public entities, and industry to develop and validate biomarkers for use as surrogate endpoints. Simon and Roychowdhury (2013) observe that a clinical biomarker must have analytical validity, clinical validity, and clinical utility for a well-defined indication. Experts note that, currently, there are two main paths to biomarker qualification: (1) sponsors negotiate with FDA one case a time, with variable information requirements depending on the biomarker, and (2) a group (such as a foundation) petitions FDA for a broad qualification of a biomarker across studies, which is often extremely burdensome because qualifications are not standardized. As such, biomarker validation can be expensive and time-consuming (Peck, 2007), though clinical trial experts agree that these costs may be offset by time and cost savings later in the development process.

During the development of sitagliptin for type 2 diabetes, biomarker use "facilitated [the] design of clinical efficacy trials" and "streamlin[ed] dose focus and optimization, the net impact of which reduced overall cycle time to filing [by 1.4 years] compared to the industry average" (Krishna, et al., 2008). These time savings were primarily driven by eliminating the Phase 2a trial, but investigators note that this may not be feasible for all drugs and/or therapeutic areas. FDA's Accelerated Approval regulations allow for drug approval based on the use of surrogate endpoints that are "reasonably likely to predict clinical benefit," and a study looking at surrogate-based clinical development programs found that the use of the Accelerated Approval pathway led to a decrease in cost to approval of 62 percent and an increase in net present value from a mean of $23 million to $72 million (Miyamoto & Kakkis, 2011).[10]

When a qualified biomarker is available for use in a clinical study, the time to enroll patients, treat them, and conduct analyses is shortened. This is because surrogate endpoint-based studies require fewer patients and less time to observe treatment effects (Miyamoto & Kakkis, 2011). These savings are most acute in Phase 2 and Phase 3 studies. Moreover, surrogate endpoints can be especially helpful for diseases with low incidence or where it is

[10] The reported figures in Miyamoto & Kakkis (2011) are based on a small subset of 15 ultra-rare diseases. Therefore, their applicability to drug development in general is questionable.

ethically difficult to do Phase 3 trials. Although experts acknowledge the time and cost savings associated with using qualified biomarkers as surrogate endpoints, many note that these savings are eroded if taking into account preclinical biomarker development and validation expenses. On the other hand, biomarker use in preclinical studies helps drugs to fail faster and sponsors to make decisions earlier. Although efficiency gains in the form of identifying nonstarters earlier are difficult to quantify, this could have a profound impact across a sponsor's development portfolio since experts estimate that 95 percent of drug ideas fail.

The primary challenge associated with using biomarkers in clinical development is the difficulty in establishing a link between a biomarker and a clinical outcome. For example, a biomarker might show something "good" (e.g., lower cholesterol), but this might not correlate with a positive clinical effect on the relevant endpoint. Given this disconnect and the time it takes to qualify a biomarker for use in a clinical study, the cost of biomarker development may outweigh the potential benefits. As such, some experts think that biomarkers are more useful in follow-on studies to complement large Phase 3 trials or in initial proof-of-concept studies. Additionally, the impact of surrogate biomarkers may not be equally transformative across therapeutic areas.

2.6 IMPROVE PATIENT, PHYSICIAN, AND PUBLIC UNDERSTANDING OF CLINICAL TRIALS AND THE VALUE OF PARTICIPATION

2.6.1 Clinicaltrials.gov Improvements

In 2000, the U.S. National Library of Medicine established ClinicalTrials.gov, a database of privately and publicly funded clinical studies conducted around the world (Anon., 2009). ClinicalTrials.gov is intended to provide "easy access to information on publicly and privately supported clinical studies on a wide range of diseases and conditions" (U.S. National Library of Medicine, 2018). It currently includes sections for patients and families, researchers, and study record managers. Sponsors or principal investigators provide and update the information on the website. In September 2016, HHS issued a "Final Rule for Clinical Trials Registration and Results Information Submission," which intends to "make it clear to sponsors, investigators, and the public which trials must be submitted, when they must be submitted, and whether compliance has been achieved" (U.S. Food and Drug Administration, 2018a).

This strategy would make more information about trials available online. It would also improve and expand upon ClinicalTrials.gov by making the site more patient-friendly and searchable for those seeking trial opportunities (Eisenberg, et al., 2011; Institute of Medicine, 2012). This strategy also involves providing online information and results in language accessible to the public (Eisenberg, et al., 2011).

Researchers agree that there are many opportunities to improve the functionality of ClinicalTrials.gov. One study recommends ensuring that online data are complete and contain useful information (Eisenberg, et al., 2011). One study also recommends cross-referencing with

patient databases (such as PatientsLikeMe) to connect eligible patients with trials (Granzyk, 2012).

Improving patient recruitment has the greatest potential to reduce the time and cost of clinical trials (Fogel, 2018). One expert recommended changing ClinicalTrials.gov into a tool to report on active trials in a way that will enable patients, caregivers, physicians, and investigators to quickly search for active trials and understand whether individual patients could meet inclusion criteria. The expert also recommended linking to a single patient registry, as well as a form in which patients can consent to be contacted about a trial.

One study recommends establishing a worldwide trial database, which would have a broader scope than ClinicalTrials.gov (Institute of Medicine, 2012; Califf, et al., 2012). There is an existing World Health Organization (WHO) database, but "unacknowledged duplicate entries make it difficult to determine a unique list of clinical trials" (Califf, et al., 2012).

2.6.2 Engage Patients in the Process of Identifying Research Questions

To help generate patient buy-in and interest in trials, this strategy would create a website in which investigators and sponsors can propose clinical questions and trials while solicitating input from patients and other stakeholders. This could involve crowd-sourcing research questions from patient forums such as PatientsLikeMe and 23andMe (Swan, 2012).

Since an estimated "30 percent of the time dedicated to clinical trials is spent on patient recruitment and enrollment" (InVentiv Health, 2013), 20 to 40 percent of registered trials fail to meet their recruitment goals (Mahon, et al., 2015; InVentiv Health, 2013), approximately 85 percent of all human clinical trials are delayed at the outset due to poor patient enrollment (Mintz, 2010), and the "original timelines for Phase 2-4 studies usually end up doubling in order to meet desired enrollment levels" (InVentiv Health, 2013), more efficient recruitment by means of greater patient engagement and accessibility could lead to substantial time and cost savings.

Researchers suggest that engaging patients in the process of identifying potential research questions could increase patients' awareness of trials and their willingness to participate (Eisenberg, et al., 2011; Hefele, et al., 2019; Sacristán, et al., 2016; Deverka, et al., 2018).

Crowd-sourced research questions have already yielded promising results. In one case, spontaneous coronary artery dissection (SCAD) patients used their patient network to "lobby for more research, presenting scientists with a ready-made collection of subjects" (Winslow, 2011). In another example, Amyotrophic Lateral Sclerosis (ALS) patients initiated a study which found that "the drug lithium failed to slow progression of symptoms, contrary to findings from an earlier small study" (Winslow, 2011).

2.6.3 Use Social Media for Patient Outreach

Social media represents a new channel for recruiting clinical trial participants. Recruitment through social media such as online support groups and other disease-specific online communities can be more efficient than traditional advertising because "social network users have actively opted-in to participate" (Mintz, 2010). As a result, these users are "more likely to favorably receive and act upon messages received through the network than they would be through unsolicited communications and traditional advertising" (Mintz, 2010).

Social media can serve as an "interactive platform that facilitates conversation with potential subjects, responses to inquiries, and gathering feedback on potential barriers to recruitment" (Andrews, 2012). As such, using social media as a recruitment and communication tool can help sponsors meet recruitment dates and milestones (Andrews, 2012; Gelinas, et al., 2017; Topolovec-Vranic & Natarajan, 2016).

Several researchers note that sponsors can improve patient recruitment through social media websites. Sponsors can use social media sites to "establish an account that specifically targets the patient population they seek" (Andrews, 2012). They can then customize their account "to describe the upcoming trial, what is involved, and how a potential volunteer can learn more" (Andrews, 2012).

A 2010 study found that social media advertising campaigns are more effective than traditional modes of advertisement because sponsors can target social media users based on their age, gender, and location (Mintz, 2010). Sponsors can also contact patients through disease-specific online health interest communities, such as TuDiabetes or Propeller Health, as well as health-based social networks with disease-specific communities, such as PatientsLikeMe (Swan, 2012; Granzyk, 2012; Wicks, et al., 2011; Mintz, 2010).

In addition to websites, sponsors can recruit patients through mobile phone applications. These applications "allow a potential subject or an investigator to search for a specific clinical trial in a therapeutic area of interest" (Andrews, 2012). Some applications are intended for general audiences; for example, one application allows users to search the National Library of Medicine "for studies being conducted all over the world" (Andrews, 2012). Other applications allow users to find trials for specific diseases (Andrews, 2012). For example, MedTrust Online's collaborated with GlaxoSmithKline to create the Cancer Trials App (Mintz, 2010).

Sponsors are also vetting Twitter as a tool for clinical study recruitment. Several patient recruitment companies use Twitter, and "a few clinical trial listing sites, including ClinicalConnection and Medpedia, tweet about ongoing and active trials" (Mintz, 2010). TrialX, a company that "attempts to match patients to specific clinical trials based on online patient-generated health records," also uses Twitter (Mintz, 2010).

In addition to improving recruitment, social media can improve communication with patients actively participating in trials. One researcher noted that social media can "support

volunteers in the course of a trial, and even afterwards during follow-up" (Andrews, 2012). For example, investigators can send updates and reminders to enrolled patients via social media (Andrews, 2012). Additionally, enrolled patients can use social media to ask questions and clarify investigator instructions (Andrews, 2012).

Using social media for recruitment poses several challenges, including confidentiality concerns, lack of clear FDA guidance, ethical and legal considerations, and potential selection bias due to multiple factors, e.g., exclusion of populations without internet access (Andrews, 2012). It can also be difficult to manage trial messaging and conversations on social networking sites and forums (Mintz, 2010).

Additionally, the efficacy of social media may be dependent upon external factors, including traditional advertising and public awareness of clinical research. Some researchers have found that social media works best when "integrated with traditional advertising methods," as "social media by itself may not be enough in most cases" (Mintz, 2010; Mahon, et al., 2015). Recruitment through social media may be limited "until the general public's understanding about the importance of clinical research is vastly improved" (Mintz, 2010).

2.6.4 Periodic Physician Updates

Physicians could play an important role in identifying and recruiting patients eligible for clinical trials. Although survey data suggest that many patients are willing to participate in clinical trials if recommended by their physicians, only 22 percent of respondents in a 2013 survey reported that a doctor or other health care professional had ever discussed medical research with them (Elsevier, 2013).

This strategy would support the development of a system to disseminate trial results to the appropriate consumers and groups in a physician-friendly, comprehensible way. For example, physicians could elect to receive periodic updates on disease-specific trial information and results (Eisenberg, et al., 2011).

Physician recommendation would likely increase enrollment in clinical trials. In one survey, nearly three-quarters of Americans said it is likely that they would "participate in a clinical trial if recommended by their doctor" (Elsevier, 2013). To facilitate this process, sponsors could use EHRs to notify physicians about upcoming trials (Eisenberg, et al., 2011).

Mahon et al. (2015) found that only 20 percent of physicians who received electronic alerts about upcoming clinical trials used these alerts to recruit patients. This suggests that sending physicians information about ongoing clinical studies (without additional education or incentives) may not alter their willingness to participate in study recruitment.

2.6.5 Patient Education and/or Campaign to Build Public Support for Clinical Research

Public awareness of the clinical trial process is generally low. In one survey, 75 percent of respondents said that they had "little to no understanding about the clinical research

enterprise and participation" (InVentiv Health, 2013). The same study also found that "less than 5 percent of Americans know where to find information about relevant clinical trials" (InVentiv Health, 2013). Limited awareness of clinical trials also leads to low participation rates. By one measure, "only 2 percent of the U.S. population participates in clinical research studies" (InVentiv Health, 2013).

While awareness of clinical trials is limited, many people report that they would be willing to participate in clinical trials if they knew about them. For example, one study found that 69 percent of respondents "wanted to take part in biobank studies" (Kaye, et al., 2015).

This strategy would provide patient education and standardized information on the purpose of clinical studies and the value of participation (Eisenberg, et al., 2011). A public campaign could help raise awareness of the clinical trial process and recruit patients. One meta-analysis found that different types of marketing, such as mass mailings and advertising, could have served as effective recruitment strategies in roughly 20 to 40 percent of the studies analyzed (UyBico, et al., 2007).

There are existing campaigns to increase support for clinical research more broadly. For example, TransCelerate BioPharma Inc. created the Clinical Research Awareness & Access Initiative, which seeks to increase "awareness of, and public engagement with, clinical research" (TransCelerate BioPharma Inc, 2016b).

Informing enrolled patients about trial results may also help convey the value of participation. Researchers report that virtually all enrolled patients want to know the results of a clinical trial (Long, et al., 2016; Terry, 2016). And one study suggests that "giving people an experience of the usefulness of their contributions and resulting advances" will increase participation in clinical trials (Terry, 2016). This finding was echoed in a 2019 conference between the Clinical Trials Transformation Initiative (CTTI) and FDA which concluded that "…engagement with patients should not just be during one discrete opportunity, but rather structured as long-term relationships that include generosity of time, transparency, and accountability" (Clinical Trials Transformation Initiative & U.S. Food and Drug Administration, 2019).

Informing enrolled patients about trial results could help convey the value of participation, but this depends on the way in which sponsors communicate trial results. For example, some enrolled patients found teleconferences useful (Augustine, et al., 2016) while others found teleconferences to be among the "least desirable dissemination methods" (Long, et al., 2016). Thus, sponsors should consider the medium used to communicate with enrolled patients. Additionally, results should be shared in a language that patients can understand (Li, et al., 2015).

2.7 CLINICAL RESEARCH WORKFORCE AND TRAINING

2.7.1 Develop Investigator Training Infrastructure and Materials

This strategy involves developing investigator training infrastructure and creating standardized core content for the training that will help ensure minimum requirements are met. A standard, thorough training curriculum could better prepare trial coordinators for the responsibilities of the job (Snyder, et al., 2016). For example, a single site coordinator could use EHRs to identify eligible patients for all ongoing trials at the site and then pass those patients along to the appropriate study team instead of having multiple coordinators at each site duplicating effort and increasing the potential of missed patients.

A standardized investigator training infrastructure would eliminate inefficiencies associated with each site creating its own training program and training its own coordinator. Standardized training and continuing education may also promote the use of innovative trial designs. Innovative designs and approaches may require complex methodologies or specialized software that would be difficult to implement if continuing education structures were not already in place.

2.7.2 Promote Expansion of the Clinical Research-capable Workforce

This strategy focuses on improved engagement and training of all parties involved in carrying out a clinical trial's day-to-day operations. The five groups primarily involved with carrying out clinical trials are investigators, community practitioners, implementers, methodologists, and the public (Institute of Medicine, 2012). Using a medical network with widespread locations to conduct a clinical trial can be more cost effective, but also means that healthcare staff, who may not have background knowledge of or experience with clinical trials, perform duties for the trial. An important component of this strategy is to educate site investigators to ensure they not only receive training but are treated as a valuable member of the team and are committed to the clinical trial, not just "handed a protocol to serve as a third-party vendor" (Christel, 2015).

This strategy could also include encouraging non-traditional contributors/sites to get involved in the clinical research enterprise. For example, clinicians with limited research experience could be trained and recruited (King Rosario, et al., 2018), and private practice settings and non-academic hospitals could be utilized as sites (Eisenberg, et al., 2011).

Academic institutions are another potential partner to engage in expanding the clinical research-capable workforce. This strategy encourages institutions to make research a central part of their missions and agendas in the short term, and in the long-term urges medical, nursing, and pharmacy schools to incorporate clinical research fundamentals into their curricula (Califf, et al., 2011). With this strategy, students would gain practical exposure to clinical trial procedures as well as gain an appreciation for the role of clinical research in the overall healthcare system.

With improved engagement and support for education about clinical trials in schools and doctor's offices, sponsors may not have to expend as much time and money to find suitable trial sites and train staff to run the trials.

2.8 REAL-WORLD DATA

2.8.1 Use of Electronic Health Records

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. Clinical trial experts note that EHRs can be useful for speeding up patient identification and recruitment, but, due to data collection and interoperability challenges, utility is limited for collecting clinical endpoints (Hills, et al., 2018). The most transformative use of EHR data may be in the development of synthetic control arms made entirely of historical data; however, this is probably 10 to 15 years away according to some experts.

EHR4CR (*Electronic Health Records for Clinical Research*) was a European project to develop "an innovative technological platform to enable the re-use of EHR data for clinical research" (Beresniak, et al., 2016). The project's cost-benefit analysis (CBA) found that, compared to current practices, the use of an EHR-based clinical research platform led to faster protocol feasibility assessment (73 to 195 days vs. 147 to 389 days), faster patient identification and recruitment (20 to 46 days vs. 40 to 100 days), and faster clinical study execution (408 to 2,737 days vs. 797 to 5,264 days). Relatedly, the CBA found that, compared to current practices, the use of an EHR-based clinical research platform led to cheaper protocol feasibility assessment ($60,388 to $160,346 vs. $120,775 to $320,692), cheaper patient identification and recruitment ($16,656 to $38,089 vs. $32,898 to $82,688), and cheaper clinical study execution ($445,696 to $2,584,512 vs. $875,032 to $4,996,728) (Beresniak, et al., 2016).

Additionally, EHR use in clinical trials could enable remote, web-based source data verification which can reduce monitoring expenditures by up to 50 percent (Uren, et al., 2013).

One clinical trials expert using EHR for patient recruitment in an ongoing study found that recruiting went from 0.5 to 1 patient per site per month to 60 patients per site per month using EHRs but noted that this is probably on the high end of what can be achieved.

The benefits of using EHRs in clinical trials accrue primarily in the early stages of a clinical study. For example, EHRs can be used for enhanced site identification, speeding up routine tasks (such as pre-populating electronic case report forms) (Beresniak, et al., 2016; Cowie, et al., 2017), and conducting protocol feasibility assessments (e.g., using algorithms to figure out how many patients meet study inclusion criteria, thus reducing the "'haystack' of individuals who might otherwise be considered for potential contact about a research study" (Granzyk, 2012). Although patients identified through EHR queries would still require research coordinator review, filtering out potential patients based on ICD-9 codes or common demographic elements can reduce coordinator workload substantially (Granzyk, 2012). On the

other hand, experts note that converting an *identified* patient to an *enrolled* patient will not necessarily be impacted by using EHRs, and that reducing the costs and timelines of enrolling patients is a much more important metric. Several experts noted that cost and time savings might be limited to label expansion and Phase 4 trials.

While most clinical trial experts associate EHR-related time and cost savings with enhanced patient identification and recruitment, one expert noted that EHRs can save substantial time when used for event/endpoint adjudication. In an event-driven trial, investigators may need to validate, for example, two events per month. In a traditional trial, that could involve having 400 patient interactions and follow-ups, whereas in an EHR-based trial, the two patients with events could be more efficiently identified via EHR.

The main challenges associated with using EHR data in clinical trials relate to the fact that the data are not validated or audited, patients may seek treatment in different healthcare facilities, data fields are often customized to meet the needs of specific hospitals or healthcare networks (thus causing interoperability issues), and, relatedly, that the substantial cost to clean up the EHR data for use in clinical study could offset the efficiency gains from using them (Coorevits, et al., 2013; Richesson, et al., 2013; De Moor, et al., 2015). For example, one expert noted that by the time you extract, clean up, and validate a patient's blood pressure data, it would probably be faster to take their blood pressure again. Moreover, even if data quality issues were addressed, the data (often unstructured) collected during routine patient care would likely differ from what is required by a research protocol (Köpcke, et al., 2013; Hersh, et al., 2013). Despite these challenges, several experts indicated that EHR data could be well-suited for clinical trials if they were linked with claims data.

With respect to using EHR data for patient identification and recruitment, one expert noted that recruitment costs are only 2 to 4 percent of Phase 2 and Phase 3 budgets, and, as such, did not expect EHR use to have a large impact on overall clinical trial costs.

2.8.2 Encourage Use of Pragmatic or Practical Clinical Trials (PCTs)

Pragmatic or practical clinical trials (PCTs) refers to a spectrum of clinical trial designs that take advantage of data routinely collected as part of standard clinical care to reduce the sample sizes, timeframes, and costs associated with traditional randomized control trials (RCTs). Embedding trial procedures within routine clinical care processes allows investigators to eliminate redundant data collection and observe "real world" outcomes that are important for patients, clinicians, administrators and policy-makers (Mentz, et al., 2016). These "real world" data reflect the diverse demographics and healthcare settings that are relevant to clinical practice as opposed to RCTs, which use highly-selected patient populations evaluated at specialized study centers (Jones, et al., 2016; Califf & Sugarman, 2015). Because PCTs have simplified operational approaches (limited site monitoring, fewer trial-specific assessments, etc.) and broader patient populations (fewer restrictions on the use of concomitant therapies, etc.), they do not generate the robust biological, pharmacokinetic, and pharmacodynamic data associated with traditional explanatory RCTs (Jones, et al., 2016; Califf & Sugarman, 2015). PCTs, as such, are commonly associated with comparative effectiveness research and other

studies that evaluate drug, medical device, and vaccine performance under "usual" conditions as opposed to tightly-controlled studies that are necessary for evaluating causal hypotheses. Experts note, however, that the distinction between pragmatic trials and explanatory trials is fluid, with studies typically incorporating elements from both.

Experts working on the ADAPTABLE trial (PCORI-funded pragmatic trial using EHR to study aspirin dosing) state that the investigation will cost $12 to $14 million, but would have cost $100 to $150 million if conducted as a traditional RCT.

Experts working on a pragmatic comparative effectiveness trial for hypertension drugs at the VA (hydrochlorothiazide vs. chlorothiazide) state the investigation will cost $5 million, but would have cost $95 to $100 million if conducted as a traditional RCT. The investigators note, however, that conducting trials within the VA network leads to substantial cost savings that would not be replicable if working across multiple healthcare networks.

There are several initiatives focused on streamlining clinical evidence generation for devices that CDRH is engaged with including NESTcc and the Virtual Patient developed by the Medical Device Innovation Consortium (MDIC). Virtual Patient is a model/framework designed to reduce clinical trial sizes by replacing the cohort of (would be) newly-enrolled control patients with data supplied from real world sources (registries, previous generation of the device, etc.). According to MDIC, Virtual Patient can reduce sample sizes by up to 50 percent, and, when sample size is reduced by 50 percent, Virtual Patient shortens the enrollment period by approximately 46 percent.

The primary benefit associated with PCTs is the potential to improve patient outcomes by quickly, cheaply, and credibly addressing gaps in clinical knowledge (QuintilesIMS Institute, 2016; Califf & Sugarman, 2015; Johnson, et al., 2014; Chalkidou, et al., 2012). Moreover, by showing benefit of treatment in "real" patients, monitoring safety data in real-world settings, and providing ongoing data for payers through "coverage with evidence development," PCTs can stimulate provider and payer interest in devices and drugs for which clinical efficacy is not well-documented (QuintilesIMS Institute, 2016; Chalkidou, et al., 2012).

Given the amount of noise in real-world data, PCTs often require large sample sizes, long study periods, and multiple trial sites to detect subtle differences in clinical outcomes. Operating clinical studies at this scale can make trial management and data quality control difficult (Cramon, et al., 2014; Chalkidou, et al., 2012). Relatedly, developing information technology infrastructure for data collection and management across multiple sites, which might all use their own data collection tools, can be resource-intensive and offset the cost and time savings associated with PCTs (Cramon, et al., 2014).

Moreover, "[good clinical practice] guidelines, governance, and consent procedures [can] substantially affect the intended simple nature" of PCTs, and complex management processes (e.g., coordinating multiple IRBs and data monitoring plans across various healthcare networks) can make clinician recruitment difficult and can add substantial time to PCTs (van Staa, et al., 2014).

Some clinical trials experts note that routine care visits are fundamentally different from clinical study visits and then attempting to embed trial procedures within a standard visit can lead to low quality data, missing data, and other inefficiencies.

2.8.3 Use Registry Data

Patient registries are collections of high-quality, standardized data from patients who use the same health services, who have the same diseases or conditions, and/or who use the same medical devices (Li, et al., 2016; Lauer & D'Agostino Sr, 2013). Data sources for registries "include patient-reported data, physician-reported data, medical chart abstraction, [EHRs], administrative databases, institutional or organizational databases, and others" (Li, et al., 2016). Registries are typically established by patient organizations for many reasons or by medical device manufacturers who use them to comply with FDA post-marketing surveillance requirements. One ongoing challenge is that registries do not exist for many therapeutic areas of interest.

Patient registries can be used for observational studies—e.g., using registry data to describe patterns and trends in health outcomes, identify outliers, detect safety signals, and assess comparative effectiveness (Lauer & D'Agostino Sr, 2013); registry-based randomized trials (e.g., combining observational data with randomized experimentation to assess comparative effectiveness in real-world settings (Lauer & D'Agostino Sr, 2013; Li, et al., 2016)—as well as a tool for enhanced patient identification and recruitment into traditional RCTs.

The registry-based Thrombus Aspiration in ST-Elevation Myocardial Infarction in Scandinavia (TASTE) trial cost "~$400,000, compared with tens of millions of dollars for a study of equivalent size using a traditional industry-funded trial model" (James, et al., 2015). Per patient costs in the TASTE trial ($50) were an estimated 90 to 98 percent cheaper than a conventional randomized control trial (Li, et al., 2016; James, et al., 2015; Fröbert, et al., 2013). The TASTE trial was performed in Scandinavia using the Swedish angiography and angioplasty registry (SCAAR) platform containing high-quality, validated EHR data. A similar platform does not currently exist in the United States.

Low per-patient costs—$16 and $40—were also reported in the registry-based Randomized Evaluation of Decolonization versus Universal Clearance to Eliminate Methicillin-Resistant Staphylococcus Aureus (REDUCE MRSA) and Cardiovascular Health Awareness Program (CHAP) trials, respectively (Li, et al., 2016; Huang, et al., 2013; Goeree, et al., 2013; Kaczorowski, et al., 2011).

A recent trial conducted at Duke University was built off an ongoing coronary stent registry. The clinical trial site only had to randomize patients and collect two additional pages of data. This registry-based approach reduced the study cost from approximately $15 million to $5 million. The patient enrollment period was reduced from 3 years to 2 years.

One expert suggested that, as a general principle, registry trials using existing data and only gathering a limited amount of trial-specific data will cost 10 percent as much as a traditional trial.

Many experts agree that patient registries can reduce patient recruitment and site identification costs. Experts note that, compared to EHRs, patient registries help improve patient identification and enrollment because many patients in registries are knowledgeable about their condition and are more likely to consent for participation. Moreover, registry data tend to be more accurate than EHR data because these data are collected for a specific purpose and are more "curated" than EHRs. When registry data can be used for collecting clinical endpoints, savings can be particularly substantial.

As they include “real world” data, registry-based trials tend to produce findings that are more generalizable than traditional RCTs (James, et al., 2015; Li, et al., 2016). Relatedly, registries allow investigators to find and enroll geographically diverse patients, adding to the generalizability of the results (Bergin, et al., 2010). One expert noted that investigators involved in registry-based trials are usually influential in their field and will advertise/push the project in a manner that further stimulates recruitment.

Several experts cite data quality and logistical challenges as the primary weaknesses associated with registry data. They note, for example, that unaudited, site-reported registries have limited use, especially those that do not collect consecutive patients. Moreover, registries often only collect data at a single point in time, which, unless updated, limits their utility. Further, many registries contain useful genotypic and phenotypic information, but they are not interconnected thus limiting their utility for large clinical trials. A centralized database such as NIH’s “All of Us” database is a step in the right direction but is still an individual effort not tied to any others. The expert noted that pharmaceutical and device companies have an incentive to keep their data separate because they are trying to use it to find new targets.

One expert who believes that patient registries do not have a substantial impact on drug trial time or cost, indicated that registry data tend to fall into a “no man’s land” for pharmaceutical clinical trials. Registries are not that helpful for first-line treatments because patients do not register before they have a disease. For second-line treatments, registry enrollment is too meager to get a representative sample of patients that will meet narrow inclusion criteria. As such, several experts believe that patient registries are only useful for label expansions and post-marketing studies.

Some experts expressed concern that market forces (i.e., registry owners charging for data usage) could offset the cost savings of using registry data for patient identification and enrollment. Most experts note, however, that data use fees are unlikely to be so high that they wipe out cost savings. They argue that database owners might charge a reasonable fee, but market will not allow them to charge exorbitant fees.

2.8.4 Utilize "Big Data" Approaches

"Big data" is an umbrella term that refers to the wide range of databases, repositories, and other technologies for aggregating and analyzing large amounts of data. As data analysis becomes more effective and accessible, the hope is that "big data" research approaches will help uncover patterns and insights that inform future clinical development decisions (Yildirim, et al., 2016; QuintilesIMS Institute, 2016; Sen, et al., 2017). Data sources include EHRs, computerized patient monitoring systems, biologic and genomic databases, patient registries, device registries, claims data, and mobile data from wearables. The 21st Century Cures Act (2016) highlights such sources of real world evidence (RWE) as playing an increasingly important role in supporting regulatory decision making, and CDRH's (2017) guidance on the "Use of Real-World Evidence to Support Regulatory Decision-Making for Medical Devices" and FDA's framework document on RWE (2018k), represent steps in FDA's effort to utilize RWE. More recently, CBER held a public workshop titled "Considerations for the Use of Real-World Evidence to Assess the Effectiveness of Preventive Vaccines" in September 2020 to establish a program to evaluate the use of RWE to support approval or to meet post-marketing requirements as per the 21st Century Cures directive (U.S. Food and Drug Administration, 2020d). Some of the case studies presented by stakeholders included the incorporation of RWE into innovative trial designs (e.g., decentralized trials, pragmatic trials) and repurposing of CDC influenza vaccine effectiveness surveillance and other data to evaluate the effectiveness of COVID-19 vaccines. The primary application of "big data" approaches is facilitating post-market surveillance and comparative effectiveness studies (Psaty & Breckenridge, 2014; Yildirim, et al., 2016). The potential benefits of using "big data" in clinical trials overlap with those discussed for EHR (Section 2.8.1), pragmatic clinical trials (Section 2.8.2), and registry-based trials (Section 2.8.3), all of which can be considered "big data" applications. Specific examples of "big data" approaches include FDA's Mini-Sentinel, which is used for post-market surveillance (Psaty & Breckenridge, 2014), PCORnet, an initiative to harness "the power of large amounts of health data and patient partnerships" for clinical trials (National Patient-Centered Clinical Research Network (PCORnet), 2016), and Big Data for Better Outcomes (BD4BO), a program to develop effective analysis of EHR data, trial data, and registry data (Yildirim, et al., 2016).

The challenges associated with "big data" depend on the specific ways in which the data are applied. As discussed in Section 2.8.1 and Section 2.8.3 in the context of EHR- and registry-based trials, data quality and interoperability issues pervade most "big data" approaches. The data collected from registries and EHR systems may be unaudited and the high customization available to EHR end users makes reconciling diverse data fields and layouts difficult. As Psaty & Breckenridge (2014) note, most big data sources "are the electronic side effects of the functions of billing and clinical care" and are not directly transferable to research applications. Available data are quickly proliferating as more functions are performed electronically, but "the noise is increasing faster than the signal" (Psaty & Breckenridge, 2014), thus offsetting the potential gains in efficiency derived from using big data approaches.

2.8.5 Looser Trial Enrollment Restrictions

Sponsors establish inclusion criteria to determine which patients are eligible to participate in a clinical trial. Some researchers claim that inclusion criteria have become too narrow, leading to unnecessarily strict enrollment criteria. For example, one study found that inclusion criteria are often "needlessly narrow to the point of making few subjects eligible, even if [there are] many subjects with the disease available" (Mahon, et al., 2015). Narrow enrollment criteria can result in recruitment delays and increased costs (Malik & Lu, 2019). Moreover, experts state that competition among researchers for patients with certain diseases or tumors can make enrollment and recruitment difficult and expensive.

Additionally, experts note that strict inclusion criteria can limit a drug's market size after approval. As a result, sponsors must attempt to strike a balance between the likelihood of approval and market size.

This strategy would encourage sponsors to carefully consider their trial enrollment criteria. Considerations might include recruitment implications and the tradeoff between purity of scientific experiment and generalizability of results to patients on other medications or with common comorbidities (i.e., internal validity vs. external validity).

Less stringent enrollment criteria could help avoid delays and reduce costs (Mahon, et al., 2015). One study recommends avoiding unnecessary criteria and reducing the number of criteria to "far less than the 50, 70, or even 100 criteria common in contemporary clinical trials" (Vickers, 2014). Another study found that conducting clinical trials with more diverse patient populations could expand the pool of research participants "without the enormous expenses and challenges entailed by current randomized controlled trial screening and sampling methods" (Richesson, et al., 2013). Using fewer inclusion criteria also makes results more generalizable, as stringent criteria can lead to "far more homogenous cohorts than are typical in real practice settings" (Richesson, et al., 2013).

When determining the appropriate number of inclusion criteria, there is a tension between internal validity and external validity, as too few inclusion criteria can make clinical effects more difficult to observe. As such, stringent inclusion criteria are often necessary for efficacy studies (Richesson, et al., 2013).

2.8.6 Encourage Sponsors to Integrate Study Designs with Clinical Practice Flows and Engage Site Investigators in the Study Design Process

Most clinical trials "take place in dedicated research centers rather than normal clinical settings" (Institute of Medicine, 2012). This limits the scope of who can participate in clinical trials (patients must live in close proximity to a dedicated clinical trial site) and adds to the time and cost of clinical investigations. If study designs were better integrated in typical clinical practice flows, trials could be conducted in more geographically diverse areas and with less redundant data capture.

The integration of all aspects of research (e.g., screening, enrollment, randomization and treatment assignment, protocol adherence, adverse events monitoring, and outcomes assessment) into routine practice workflows and data-capture mechanisms" allows for the "rapid execution of high-impact demonstration projects" (Richesson, et al., 2013).

Experts observe that integrating clinical trials into "normal" clinical practice is easier said than done. Though integrating a case report form into a standard clinical workflow is feasible, experts maintain that a clinical visit is fundamentally different from a trial follow-up, thus limiting the amount of study-specific data that can be generated from a "real world" visit.

2.9 ENCOURAGE ADAPTIVE DESIGN

Adaptive design refers to a range of clinical trial methodologies that allow changes to key design features based on observed (unblinded) data while studies are ongoing (Yildirim, et al., 2016; Korn & Freidlin, 2017). Adaptive designs are used in both exploratory and confirmatory clinical trials. Exploratory adaptive designs focus primarily on finding safe and effective doses or with dose-respond modeling, and confirmatory adaptive designs involves "making prospectively planned changes to the future course of an ongoing trial on the basis of an analysis of accumulating data from the trial itself" (Bhatt & Mehta, 2016). As conducting interim analyses on unblinded data can pose statistical and ethical challenges, adaptive designs "require careful attention to statistical techniques and operational procedures to ensure that the implementation is…free from bias" (Bhatt & Mehta, 2016).

Simple adaptive designs, such as early termination due to futility, are used on about 20 percent of clinical trials, and more sophisticated adaptive designs, such as adaptive dose ranging and seamless Phase 2-3 studies, are used more rarely, in about 5 percent of clinical trials (Getz, 2014; Getz, et al., 2013). Other adaptive designs include adaptive group sequential design (i.e., increasing the number of patients in promising trial arms and/or terminating futile trial arms) and biomarker-driven adaptive population-enrichment designs (i.e., prospectively creating biomarker-positive and -negative subgroups of patients and increasing—or terminating—enrollment based on interim analysis) (Bhatt & Mehta, 2016).

David et al. (2015) conducted an analysis of the impact of seamless Phase 2-3 adaptive design on clinical trial size, probability of success, time to market, expected net present value (ENPV), time to first get-out, and cost to first-get out. The authors explored how seamless Phase 2-3 designs can incorporate one interim analysis if the goal is to maximize value (scenario 1) or two interim analyses if the goal is to "shorten the time to the first opportunity to make clinical data-based decisions" (scenario 2). Assuming a base case of 459 patients, 59 percent probability of success (POS), time to market if successful of 8.75 years, expected net present value (eNPV) of $5.1 million, time to first get-out of 36 months, and cost to first get-out of $10.6 million, they projected the following results. For scenario 1, they projected 393 patients, 75 percent POS, time to market if successful of 5.08 years, eNPV of $42.3 million, time to first get-out of 31 months, and cost to first get-out of $28.6 million. For scenario 2, they projected the following results: 316 patients, 59 percent POS, time to market if successful of 4.92 years,

eNPV of $34.9 million, time to first get-out of 17 months, and cost to first get-out of $12.2 million (David, et al., 2015). These findings are consistent with Cuffe et al. (2014) and Senchaudhuri (2015), who found that seamless Phase 2-3 designs can speed up clinical trials by 1-2 years and reduce patient sample sizes by over 30 percent, respectively. Seamless proof-of-concept and dose-finding trials can also create efficiencies, in one case reducing trial time by approximately 9-12 months and trial patient population by 100 fewer patients (Senchaudhuri, 2015).

Although some experts note that adaptive designs can save time and money when used in Phase 3 studies, most experts found adaptive designs to be most cost-effective when used in the early phases of clinical development. They note that quickly dropping futile trial arms and ramping up enrollment in optimal sub-segments of patients can dramatically impact Phase 1 success rates and lead to more successful Phase 2 studies. The ability to "drop the loser" in Phase 1 and/or "extend accrual to expand statistical power or rationally expand arms to be more inclusive" is especially helpful when you do not have a strong hypothesis about which population a drug will work for when appropriate study size is difficult to estimate. Several experts noted that these benefits would be especially profound in early-stage oncology trials.

Two experts stated that adaptive designs might not improve the probability of success of an individual trial but would help the entire drug program by helping sponsors get rid of unpromising approaches more quickly. They also note that adaptive design can help sponsors move more cost-effectively between studies. Since adaptive design allows sponsors to test multiple hypotheses (or even products) at once, they can quickly launch follow-on studies for promising doses/products that take advantage of existing trial infrastructure such as site contracts, databases, protocols, and more. The traditional approach of stopping the initial trial, analyzing the data, and then opening a new trial would take too long to utilize the existing infrastructure.

The primary challenge associated with sophisticated adaptive designs is that there is limited interest in using them among large pharmaceutical companies and small pharmaceutical companies. For large companies, the frontloaded expenses of adaptive design (statistical analyses, IT infrastructure, etc.) can drive a wedge between finance and research teams who debate its cost-effectiveness, and there can be reluctance to use novel statistical approaches among senior managers who may not want to take the (perceived) risk of being the first company to use a novel regulatory strategy. Moreover, research budgets are typically divided into Phase 2a and before and Phase 2b and after, so it can be difficult for a research team doing a combined Phase 2-3 study to compete for internal resources with a team doing a traditional Phase 3 study. For small companies, the primary goal is to be acquired or go public, so thinking about a combined Phase 2-3 trial is too far down the road to be an immediate concern.

Contributing to pharmaceutical companies' reluctance to use adaptive design is the perception that FDA does not endorse sophisticated statistical approaches. One expert noted that adaptive designs are more burdensome for FDA reviewers—taking 2-3 weeks to review vs.

4 hours for a traditional study—and another expert stated that FDA does not endorse adaptive designs because FDA is concerned that they might miss important safety data if patients/trial arms are dropped out of the study partway through.

Other experts noted that adaptive designs (such as early stopping for futility) are already widely in use and that other adaptive approaches would only lead to incremental benefits. Faster timing to first decisions will help weed out nonstarters more quickly, but adaptive designs often call for a subsequent enlargement of promising trials arms thus offsetting the time and cost savings gained from reaching the first get-out decision more quickly (Yildirim, et al., 2016).

2.10 STANDARDIZED CONTRACTS

Clinical trial contracts ensure that "all parties involved in the performance of the clinical trial are offered the protections they need" (Thompson, et al., 2016). They help sponsors protect intellectual property, access data, and ensure that sites comply with protocols (Thompson, et al., 2016). They also help sites protect their patients' safety and provide practices with fair compensation (Thompson, et al., 2016).

While contracts provide important protections, the contract negotiation process is often time-consuming. Impediments and inefficiencies in the process can slow trial startup and affect patient access to therapies in development (Vose, et al., 2016). For example, a 2015 survey found that contract negotiations with contract research organizations (CROs) are one of the top three burdens to research sites among the American Society of Clinical Oncology and the American Society of Clinical Investigation (Vose, et al., 2016). According to another survey, 44.1 percent of community-based physician investigators and research staff said that CROs made the contract negotiations process more difficult for their research program (Thompson, et al., 2016).

This strategy would help develop, disseminate, and encourage the use of standardized contracts. These contracts can be pre-negotiated to address any major issues between potential sponsors and networks, leaving only a few project-specific details to be settled. Templates for trial agreements can be posted online (Eisenberg, et al., 2011).

According to experts, the existing contract process can require two to six months of negotiation. In one example of Accelerated Clinical Trial Agreement (ACTA), the process was shortened from 76 days to 14-21 days when sponsors required legal review; if sponsors did not require legal review, negotiations were shortened even further to 3-4 days. Another study found that use of standard agreements reduced final contract negotiation times by 33 days on average. The same study found that using previously negotiated terms reduced final contract negotiation by an average of 22 days (Kiriakis, et al., 2013). A program that issued no-negotiated contracts (as well as other interventions) enrolled patients 100 percent faster than existing trial sites (Christel, 2015).

Many experts state that the contract negotiation process requires a significant amount of time, and that using standardized contracts would help reduce time and costs. One expert noted that savings would likely be greatest during Phases 2 and 3. Another expert suggested that standard contracts certified by the Association of Academic Health Centers and accepted by Academic Medical Centers across the United States would yield the most significant savings. Additionally, one expert recommended establishing a maximum allowable time for contract negotiations as part of the site accreditation process to incentivize efficient contract negotiation. Another expert recommended incorporating standardized contracts with centralized IRBs to maximize enrollment efficiency for multi-center trial start up.

There are several existing efforts to provide standardized contracts. The National Cancer Institute and CEO Roundtable on Cancer jointly developed standardized contracts based on areas of convergence across clinical trial agreements (National Cancer Institute, 2008). Additionally, Model Agreements and Guidelines International also created standard templates for clinical trial agreements with input from contract negotiators and attorneys (Model Agreements and Guidelines International, 2017). Legal experts from institutions and industry jointly developed the Accelerated Clinical Trial Agreement (ACTA), which now has five active pilot projects (Accelerated Research Agreements, 2017a; Accelerated Research Agreements, 2017b). Finally, the Collaborative Institutional Training Initiative (CITI) Program provides free four modules to subscribing organizations that explain contract development, negotiation, and execution (Collaborative Institutional Training Initiative, 2020).

Some experts stated that using standardized contracts would only reduce time and costs modestly. They noted that savings would vary based on the length of the study, and that because the extra time needed for contract negotiation is limited to start-up, this strategy might not reduce overall trial time. One expert noted that sites and sponsors could still have legal conflicts even when using standardized contracts. Disagreements and litigation can still arise regarding the duration of confidentiality agreements, intellectual property terms, publication rights, liability and indemnification, or research-related injuries (Eapen, et al., 2013; Vose, et al., 2016). Thus, even when using standardized contracts, other legal issues can still occur and potentially offset the time saved by standardized contracts.

2.11 CLINICAL TRIAL NETWORKS

2.11.1 Engage Regulatory Bodies, Industry, Researchers, and Others in Collaborative Initiatives

Collaborative initiatives create an opportunity for a diverse group of stakeholders to brainstorm collectively about improving the efficiency of clinical trials. Potential collaborators include regulatory bodies, the pharmaceutical industry, researchers, and others who can work together to identify inefficiencies and incentives and formulate new business models (Kramer & Schulman, 2011). Government funding for a network of academic and industry researchers with the same clinical focus is one possible engagement method (Califf, 2006).

Numerous collaborations exist as potential spaces for multidisciplinary discussion and research to improve clinical trial efficiency. One example is the Clinical Trials Transformative Initiative (CTTI), which is developing evidence-driven clinical trial practices (Clinical Trials Transformation Initiative (CTTI), 2016; Vickers, 2014). Another example is the NIH Health Care Systems Research Collaboratory, whose goal is to improve clinical trial processes by "creating a new infrastructure for collaborative research with healthcare systems" (National Institutes of Health Health Care Systems Research Collaboratory, 2016). The National Patient-Centered Clinical Research Network (PCORnet) uses large amounts of health data and partnerships with patients to reduce the cost burden and effort required to conduct clinical trials, and TransCelerate BioPharma Inc. aims to foster collaboration between the biopharmaceutical research and development communities. CDRH also participates in several collaborative communities comprised of multiple stakeholders. These include Collaborative Community on Ophthalmic Imaging, Standardizing Laboratory Practices in Pharmacogenomics Initiative (STRIPE) Collaborative Community, International Liquid Biopsy Standardization Alliance (ILSA), Xavier Artificial Intelligence (AI) World Consortium among others (U.S. Food and Drug Administration, 2021b).

Collaborative initiatives can lead to faster "discovery and development of innovative therapeutics" (Amiri & Michel, 2015), which also has the potential to reduce clinical trial costs.

2.11.2 Develop and Support Permanent Networks of Resources that will Provide Consistent Trial Infrastructure

Federal assistance in the development and support of continuously-funded and permanent resource networks to replace the current ad hoc method of conducting clinical trials in the U.S. could help provide consistent trial infrastructure (English, et al., 2010; Eisenberg, et al., 2011). These permanent networks of resources would be designed to evaluate "a series of interventions, including investigational therapies or preventives," with standardized data collection and protocols (Eisenberg, et al., 2011). The networks can include research sites, investigators, support staff, experts, regulatory consultants, and community medical practitioners, which would be organized around disease/practice areas ("nodes") on a regional or national scale. However, due to resource requirements a disease-specific network may not make sense when the trial's target disease is less common. In these cases, networks that can support clinical research across a wide range of diseases, such as the Clinical and Translational Science Awards (CTSA) consortium, may be a better option (Eisenberg, et al., 2011). Another possible network set-up could be a "hub and spoke" arrangement between larger medical centers and community health care providers (Eisenberg, et al., 2011; Institute of Medicine, 2012). The goal of these networks would be to demonstrate quality and efficiency in patient enrollment and trial implementation (English, et al., 2010).

Both the federal government and network users would share the cost of maintaining resource networks. The infrastructure would receive continuous federal funding support, preferably through more permanent contracts, rather than grants, and those conducting health care-related scientific research would have access to these networks in exchange for a fee (Eisenberg, et al., 2011; English, et al., 2010).

The success of these resource networks would depend on inclusion of and support from the community. Including community practitioners with appropriate support and infrastructure could "increase patient access to trials, trial accrual, and engagement of the medical community in evidence-based medicine" (Eisenberg, et al., 2011). A "virtual coordinator" could also support several community practice sites in a given network in their research participation (Eisenberg, et al., 2011).

Permanent resource networks could also encourage data sharing in the pharmaceutical industry. For example, a GlaxoSmithKline (GSK) initiative aims to avoid repeating mistakes by releasing patient-level data from both successful and failed drug clinical trials (Harrison, 2012). Other data types that would be valuable to share among networks include "study protocol, statistical analysis plan, completed case report forms, company marketing assessments and internal company correspondence" (Harrison, 2012).

There are numerous examples of permanent resource networks in action. One is the Health Care Systems Research Network (HCSRN, formerly HMORN), which includes several disease networks that are focused on topics such as vaccine safety, cancer, cardiovascular diseases, and mental health (Institute of Medicine, 2012). The Immune Tolerance Network (ITN) Trial Share and the Pooled Resource Open-access ALS Clinical Trials (PRO-ACT) are also working to develop clinical trial data sharing networks (Mullard, 2013). Lastly, there is a national network of sites testing multiple therapies for molecularly-defined sets of cancers in oncology umbrella trials (Mullard, 2014; Mandrekar, et al., 2015).

Experts note that clinical trial networks and their capacity for data-sharing would help remove much of the redundancy in the trial start-up process and during trial monitoring, which would reduce trial length. Permanent resource networks could also minimize costs incurred by sponsors through the availability of standardized data collection and protocols across sites (Eisenberg, et al., 2011).

2.12 CENTRALIZED INSTITUTIONAL REVIEW BOARDS (IRBS)

Institutional review boards (IRBs) play an essential role in keeping human subjects safe during clinical trials. Before a clinical trial begins, IRBs ensure that the clinical trial protocol is appropriate and that the benefits to study participants outweigh the risks. Once clinical trials are underway, IRBs at each clinical trial site monitor protocol implementation and ensure that the trial is carried out in accordance with relevant regulations and good clinical practice guidelines.

In 2006, FDA issued regulations and guidance on the use of centralized IRBs that allow "institutions involved in multi-institutional [drug] studies… [to] use joint review, reliance upon the review of another qualified IRB, or similar arrangements aimed at avoidance of duplication of effort" (21 CFR 56.114) (U.S. Food and Drug Administration, 2006b). Currently, NIH requires all sites participating in multi-site studies that involve non-exempt human subjects research funded by the NIH to use a single IRB on those applications with due dates January 25, 2018 and beyond (National Institutes of Health, 2020). Further, Section 3056 of the 21st Century

Cures Act enacted in 2016 modified statute to remove requirement for review by "local" institutional review committee for device studies, thereby making it possible to use centralized IRBs in medical device trials.

Given the push towards use of centralized IRBs, there is some evidence that their use is gaining some traction in drug clinical trials; although barriers still exist for widespread adoption (Flynn, et al., 2013). For example, a study by Tamariza et al. (2019) report that 61 percent of all sites for the Systolic Blood Pressure Intervention Trial conducted at 102 sites used centralized IRBs. One expert indicated that NIH and Department of Veterans Affairs (VA) are currently using centralized IRBs for some clinical trials. However, the use of centralized IRBs in medical device trials is still few and far between.

According to a complex medical device expert, it can take between three and eight months to complete local IRB reviews, depending on device complexity and whether the IRBs have questions. A centralized IRB would reduce this timeframe by 50 percent. Experts agree that IRB costs are significant (approximately $6,000 per site) and that centralization would help reduce costs. In addition to direct savings on IRB fees, centralized IRBs would reduce time to study approval at multiple sites, thus shortening enrollment periods and reducing costs (Seehusen, et al., 2018). The cost and time savings of using centralized IRBs would be especially impactful for large, distributed trials. One complex medical device expert indicated that it would be helpful for FDA to better publicize its recent decision allowing medical device trials to use centralized IRBs since historically device trials have had to use local IRBs.

Two experts indicated that IRB-associated costs and delays are not as pronounced as they once were, implying that the costs of centralized IRBs might outweigh the benefits. Additionally, if centralized IRBs approve clinical trial sites serially instead of in parallel, potential cost and time savings would be mitigated.

2.13 CDC/NIH COLLECTION OF EPIDEMIOLOGICAL DATA

Vaccine clinical trials must meet stringent standards of safety and efficacy because the diseases treated by vaccines have high transmission rates and major public health implications. To support such robust studies, vaccine developers typically spend substantial time and tens of millions of dollars across programs trying to collect epidemiological data on disease incidence in the earliest stages of a clinical trial. However, CDC/NIH already collects much of this epidemiological data, and if it were made available in a shared preclinical database, it could save vaccine manufacturers money and time.

The main benefits associated with this strategy are reductions in preclinical trial costs and duration. In addition to individual developers saving time and money by utilizing a shared CDC/NIH epidemiological database, this strategy could also reduce the likelihood of multiple vaccine manufacturers expending effort collecting the same or similar data. One expert noted that a database of this type could only provide limited cost and time savings after Phase 1 and would not impact trials' probability of success. Another said that efficiency gains would vary by disease; it is easier for vaccine companies to collect data on prevalent diseases like the flu

compared to lower incidence diseases, for which data collection would require more time and effort.

2.14 SUPPORT FOR CGMP-COMPLIANT MANUFACTURING FACILITIES

This strategy involves increasing government support for current good manufacturing practice (cGMP) compliant facilities in the U.S. in which vaccines are produced. There are very few cGMP-compliant bioproduction facilities operating in the U.S.; one expert stated that there are only six U.S. facilities that can manufacture vaccine bioproducts for Phase 1 trials and no facilities with the capacity to handle Phase 2 trials. Vaccines must be produced in cGMP-compliant facilities before they can be given to human patients during a clinical trial, so the lack of these facilities can interrupt clinical development programs and make the manufacturing process more expensive. Domestic facilities would be easier to regulate and monitor than those located overseas and would decrease the likelihood that trials are interrupted by delays in vaccine manufacturing.

One expert said this strategy would significantly reduce the cost burden of conducting vaccine clinical trials and could potentially aid the national strategy for pandemic preparedness. FDA's advanced manufacturing efforts, which include funding to support manufacturing of biologics and the advancement of continuous manufacturing and 3D printing technologies, are expected to improve vaccine manufacturing capacity in the U.S. For example, FDA is currently investigating recombinant vaccine manufacturing processes with potential to increase yield and reduce costs (U.S. Food and Drug Administration, 2021d).

3 ESTIMATING THE POTENTIAL IMPACT OF SELECT STRATEGIES ON DEVELOPMENT COST, DURATION, AND PHASE TRANSITION SUCCESS PROBABILITY

The literature review and accompanying expert interviews only offered limited quantitative information that can be used to estimate the impact of a given strategy on cost, duration, and phase transition success probability of drug, preventive vaccine, or therapeutic complex medical device development. Thus, we assembled a panel of 27 experts to elicit this information in a more structured manner. Below we provide further detail on the expert opinion elicitation process and the results obtained.

3.1 STRATEGY SELECTION FOR EXPERT OPINION ELICITATION

We relied primarily on the findings from our literature review and interviews described in Section 2 to select the most promising strategies (i.e., strategies with quantitative data we could use for modeling impacts) for inclusion in the expert opinion elicitation (Table 3). We also included those strategies that were specific to preventive vaccine and therapeutic complex medical device development even though the literature did not provide any studies with any actionable data. This resulted in a selection of 14 strategies depicted in Table 1.

Table 3. Strategies Selected for the Expert Opinion Elicitation

Abbreviated Strategy Title	Strategy	Applicable to		
		Drugs	Preventive Vaccines	Therapeutic Complex Medical Devices
Mobile Technologies	2.1.2. Wider Use of Mobile Technologies, Including Electronic Data Capture	✓	✓	✓
Simplified Clinical Trial Protocols and Reduced Amendments	2.2.1. Simplified Clinical Trial Protocols and Reduced Amendments	✓	✓	✓
Reduced SDV	2.2.2. Reduced Source Data Verification (SDV)	✓	✓	✓
Improvements in FDA Review Efficiency and Interactions	2.4.3. Improve the Predictability of the Review Process by Setting Firm Targets and Commitments	✓	✓	✓
	2.4.4. Engage in More Frequent and Timely Interactions with Industry	✓	✓	✓
Staged Approval	2.4.7. Staged Approval Process	✓	✓	✓
Biomarkers as Surrogate Endpoints	2.5. Biomarkers as Surrogate Endpoints	✓	✓	✓
Electronic Health Records	2.8.1. Use of Electronic Health Records	✓	✓	✓
Patient Registries	2.8.3. Use Registry Data	✓	✓	✓
Adaptive Design	2.9. Encourage Adaptive Design	✓	✓	✓
Standardized Contracts	2.10. Standardized Contracts	✓	✓	✓
Centralized IRBs	2.12. Centralized Institutional Review Boards (IRBs)			✓
CDC/NIH Developing Epidemiological Data on Disease Incidence	2.13. CDC/NIH Collection of Epidemiological Data		✓	
Federally-supported cGMP-compliant Manufacturing Facilities	2.14. Support for cGMP-Compliant Manufacturing Facilities		✓	

We combined two of the related strategies into one category, Improve the Predictability of the Review Process by Setting Firm Targets and Commitments (2.4.3) and Engage in More Frequent and Timely Interactions with Industry (2.4.4) into Improvements in FDA Review Efficiency and Interactions, as the two are related and we did not think that experts would be able discern different impacts for each category separately. This resulted in a total of 13 strategies to be evaluated by our panel.

3.2 EXPERT OPINION ELICITATION

3.2.1 Expert Panel

In accordance with recommended best practices in Knol et al. (2010), we used literature review, citation analysis, and recommendations by other experts (i.e., snowball method) to identify individuals with expertise in drug, vaccine, and/or medical device development, biomedical or clinical research, health or pharmaceutical economics, and health policy. This research yielded nearly 120 experts for our initial convenience sample. We prioritized this list based on the type of expertise needed (e.g., representation across therapeutic areas and types of medical products, drugs, preventive vaccines, and therapeutic complex medical devices) and aimed for a panel between 25-30 experts. Of the 120 experts, we selectively targeted experts and were able to recruit a total of 27 to participate in the study.[11] Among the experts that agreed to participate, 8 (30 percent) had expertise in drug development only; 2 (7 percent) in preventive vaccine development only; 5 (19 percent) in therapeutic complex medical device development only; and the remaining 12 (44 percent) had expertise in more than one area.

3.2.2 Elicitation Protocol

We developed an online questionnaire (see Appendix A) designed to elicit each expert's opinion on the potential of those strategies depicted in Table 3 to streamline the drug, preventive vaccine, and therapeutic complex medical device development processes. Specifically, for each of the 13 strategies, we asked the expert panel to quantify its potential impact on cost, duration, likelihood of phase transition success (in percentage terms) associated with each development stage (i.e., non-clinical, Phase 1, Phase 2, Phase 3, FDA review, and Phase 4 for drugs and preventive vaccines; non-clinical, feasibility study, pivotal study, FDA review, and post-approval for complex medical devices). We geared the questions toward the area of expertise of the panel member. For example, those experts with expertise in the medical device industry only had to answer those questions applicable to therapeutic complex medical devices. We also requested best professional judgment estimates regarding the cost, duration, and phase transition success probabilities for preventive vaccines and therapeutic complex medical devices.

[11] Because the number of experts exceeded 9, the number allowed under the Paperwork Reduction Act, we obtained clearance from the Office of Management and Budget (OMB) for the information collection under ASPE's generic clearance, *ASPE Generic Clearance for the Collection of Qualitative Research and Assessment OMB No. 0990-0421*.

We pilot tested our questionnaire and protocol with 3 experts. As a result of this pilot, we refined our questionnaire to eliminate ambiguities in question wording and added clarifying instructions. In general, we asked about the same clinical trial phases for each strategy, however, in the drug questionnaire, based on expert feedback received during pilot testing, we treated two strategies (Electronic Health Records and Patient Registries) differently. For these two strategies, we included two additional phases: Phase 3L (label expansion) and 3N (new drugs). We gave the experts the option of providing undifferentiated Phase 3 estimates if they were unable to distinguish between Phase 3L and Phase 3N. Phase 3L and Phase 3N for strategies other than Electronic Health Records and Patient Registries were not deemed relevant by our experts and thus not included for the other strategies.

We fielded the questionnaire on February 21, 2018 and received responses by March 7, 2018. We aggregated responses to create group averages and then provided the group summary to each expert along with their original responses. The objective of this iteration round, conducted from April 12, 2018 through April 25, 2018, was to give each expert the opportunity to revise their original responses in light of the group averages if they saw fit. Additionally, we conducted follow-up interviews with select experts to clarify their responses and to ask additional questions about the estimates they provided. Table 4 through Table 6 present our findings for drugs, preventive vaccines, and complex medical devices. Appendix B delineates the expert estimates presented in Table 4 by therapeutic area.

We acknowledge that our expert elicitation could not capture every nuance of the clinical development process. We asked participating experts to envision a “typical” clinical trial and to focus on the broad elements of clinical trials most likely to impact cost, duration, and phase transition success probability. While simplification was necessary for generating generalizable benchmark data, subtle differences between clinical trial types and biopharmaceutical development programs may have been lost.

Table 4. 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
Centralized IRBs [a]	Non-clinical	NA	NA	NA
	Phase 1	NA	NA	NA
	Phase 2	NA	NA	NA
	Phase 3	NA	NA	NA

Strategy	Phase	Cost	Duration	Success Likelihood
	FDA Review	NA	NA	NA
	Phase 4	NA	NA	NA
CDC/NIH Developing Epidemiological Data on Disease Incidence [b]	Non-clinical	NA	NA	NA
	Phase 1	NA	NA	NA
	Phase 2	NA	NA	NA
	Phase 3	NA	NA	NA
	FDA Review	NA	NA	NA
	Phase 4	NA	NA	NA
Federally-supported cGMP-compliant Manufacturing Facilities [b]	Non-clinical	NA	NA	NA
	Phase 1	NA	NA	NA
	Phase 2	NA	NA	NA
	Phase 3	NA	NA	NA
	FDA Review	NA	NA	NA
	Phase 4	NA	NA	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.

[a] Strategy only considered for therapeutic complex medical device development.

[b] Strategy only considered for preventive vaccine development.

Table 5. Expert Estimates of Strategy Impacts on Cost, Duration, and Probability of Phase Transition Success for Preventive Vaccines

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

Strategy	Phase	Cost	Duration	Success Likelihood
	Phase 3	-15%	-14%	10%
	FDA Review	0%	0%	4%
	Phase 4	0%	0%	NA
Electronic Health Records	Non-clinical	0%	0%	0%
	Phase 1	0%	0%	0%
	Phase 2	-2%	-1%	0%
	Phase 3	-2%	-1%	6%
	FDA Review	0%	0%	6%
	Phase 4	0%	0%	NA
Patient Registries	Non-clinical	0%	0%	0%
	Phase 1	0%	0%	0%
	Phase 2	0%	0%	0%
	Phase 3	0%	0%	0%
	FDA Review	0%	0%	0%
	Phase 4	0%	0%	NA
Adaptive Design	Non-clinical	0%	0%	0%
	Phase 1	0%	-4%	0%
	Phase 2	-1%	-5%	0%
	Phase 3	-2%	-2%	0%
	FDA Review	0%	0%	0%
	Phase 4	0%	0%	NA
Standardized Contracts	Non-clinical	0%	0%	0%
	Phase 1	0%	-2%	0%
	Phase 2	0%	-2%	0%
	Phase 3	0%	-2%	0%
	FDA Review	0%	0%	0%
	Phase 4	0%	0%	NA
Centralized IRBs [a]	Non-clinical	NA	NA	NA
	Phase 1	NA	NA	NA
	Phase 2	NA	NA	NA
	Phase 3	NA	NA	NA
	FDA Review	NA	NA	NA
	Phase 4	NA	NA	NA
CDC/NIH Developing Epidemiological Data on Disease Incidence [b]	Non-clinical	0%	0%	0%
	Phase 1	0%	0%	0%

Strategy	Phase	Cost	Duration	Success Likelihood
	Phase 2	0%	0%	0%
	Phase 3	-1%	-1%	0%
	FDA Review	0%	0%	0%
	Phase 4	0%	0%	NA
Federally-supported cGMP-compliant Manufacturing Facilities [b]	Non-clinical	0%	0%	0%
	Phase 1	-8%	0%	0%
	Phase 2	-8%	0%	0%
	Phase 3	-8%	0%	0%
	FDA Review	0%	0%	0%
	Phase 4	-16%	0%	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.

[a] Strategy only considered for therapeutic complex medical device development.

[b] Strategy only considered for preventive vaccine development.

Table 6. Expert Estimates of Strategy Impacts on Cost, Duration, and Probability of Phase Transition Success for Therapeutic Complex Medical Devices (CMDs)

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

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

NA = Not applicable

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

[a] Strategy only considered for therapeutic complex medical device development.
[b] Strategy only considered for preventive vaccine development.

4 CONCLUSIONS

There are several limitations to this environmental scan. 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 (see questionnaire in Appendix A), 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.

We will use findings from this scan along with analytical models of drug, preventive vaccine, and therapeutic complex medical device development costs to estimate the likely impact of each strategy on development costs. Despite the limitations of expert opinion based estimates, we think their use in this manner will allow useful comparisons across medical products of interest. See for example, the results of the ASPE-funded study, "Therapeutic Complex Medical Device Development" and Sertkaya et al. (2022).

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APPENDIX A – EXPERT ELICITATION QUESTIONNAIRE

INTRODUCTION

Thank you for logging on to this important HHS questionnaire. This questionnaire is being administered by HHS's contractor, Eastern Research Group, Inc. (ERG). Your responses and participation in this questionnaire are CONFIDENTIAL. ERG will compile the aggregated results; no individual responses will be identified to HHS.

The purpose of this questionnaire is to solicit information related to clinical trials (e.g., study costs, clinical trial times, likelihood of success) as well as your opinion on potential strategies that may help improve their efficiency. Your responses will help HHS assess:

- The most promising innovations and methods for clinical trial development,
- Barriers to the implementation of more efficient methods,
- Policy tools that can streamline clinical trials and their potential impact in reducing clinical trial costs and clinical trial times and/or improving likelihood of success, and
- Typical costs for novel drug, vaccine, and complex medical device clinical trials

The questionnaire should take 45 minutes or less of your time. The questionnaire software will save your responses as you move from page to page, so if you are interrupted, when you log in again you can start where you left off.

KEY TERMS

The following terms are used extensively throughout this questionnaire. Please take the time to review and understand their definitions. If you have any questions or concerns, please contact XXX at XXX@erg.com.

Clinical Trial Cost: Estimated average total cost of a single clinical trial study.

Clinical Trial Time: Estimated average time from inception to the completion of the study report for a single clinical trial study.

Phase Transition Success Probability: Likelihood that the clinical trial study will be successful, allowing the sponsor to transition to the next phase.

SCREENER FOR AREA OF EXPERTISE

1. Which type of clinical trials are you familiar with? *Please check all that apply*.

   - ❒ Drugs, including biologics and therapeutic vaccines
   - ❒ Preventive vaccines
   - ❒ Complex medical devices – These include all devices that require FDA premarket approval (PMA).

DRUGS, INCLUDING BIOLOGICS AND THERAPEUTIC VACCINES

The following questions are related to drugs, including biologics and therapeutic vaccines.

Below is a list of strategies as available from published literature that could potentially improve clinical trial efficiency by reducing clinical trial cost, clinical trial time, or increasing the probability of phase transition success.

On the following pages, we will ask for more detailed information about the impact of each strategy on clinical trial cost, clinical trial time, and phase transition success probability.

2. Which of the following strategies do you think could impact the clinical trial cost, clinical trial time and/or phase transition success probability of a clinical trial study?

   - ❒ **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 as 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.
- ❒ **Staged approval:** Staged approval could entail granting provisional marketing approval to market a drug, complex medical device, or preventive vaccine after safety and basic efficacy have been shown, and then continuing to collect additional safety and efficacy data. This would reduce the threshold for initial approval, perhaps with a limited patient population, and then gradually expand it as more data are collected.
- ❒ **Biomarkers as surrogate endpoints:** Biomarkers as surrogate endpoints are biological indicators that may correlate with the desired clinical endpoint, for example when it would take a long time for the clinical endpoint to become evident. The strategy could entail clarifying the path to biomarker validation or encouraging collaboration between academics, public entities, and industry to develop and validate biomarkers for use as surrogate endpoints.
- ❒ **Electronic health records:** EHRs, used here as being synonymous with electronic medical records (EMRs), are digital versions of the data collected when a patient visits a healthcare provider's office. The strategy could entail encouraging sponsors to use EHRs for patient and physician recruitment or to collect clinical endpoints.
- ❒ **Patient registries:** A patient registry is an organized system that uses observational study methods to collect uniform data to evaluate specified outcomes of a disease or condition for a population. Registries include those established by a patient organization for a particular disease as well as registries that are sometimes established by the manufactured 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.
- ❒ **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.

On the following pages, you will be asked about the impact of these strategies on the clinical trial cost, clinical trial time, and phase transition success probability. You will see a matrix like the one below.

EXAMPLE

For each of the clinical phases listed, please estimate the average impact of **STRATEGY X** on the cost of a clinical trial study, the clinical trial time, and phase transition success probability, as applicable. If you do not expect **STRATEGY X** to have an impact on a particular phase or element, please leave the estimated impact at 0%.

	Clinical Trial Cost (%)	**Impact is a(n)...**	**Clinical Trial Time (%)**	**Impact is a(n)...**	**Phase Transition Success Probability (%)**	**Impact is a(n)...**
Non-Clinical Phase	____%	Increase/Decrease	____%	Increase/Decrease	____%	Increase/Decrease
Phase 1	____%	Increase/Decrease	____%	Increase/Decrease	____%	Increase/Decrease
Phase 2	____%	Increase/Decrease	____%	Increase/Decrease	____%	Increase/Decrease
Phase 3	____%	Increase/Decrease	____%	Increase/Decrease	____%	Increase/Decrease
Phase 3 - New Drugs	____%	Increase/Decrease	____%	Increase/Decrease	____%	Increase/Decrease
Phase 3 - Label Expansions	____%	Increase/Decrease	____%	Increase/Decrease	____%	Increase/Decrease
FDA NDA/BLA Phase	____%	Increase/Decrease	____%	Increase/Decrease	____%	Increase/Decrease
Phase 4	____%	Increase/Decrease	____%	Increase/Decrease	____%	Increase/Decrease

3. To which of the following therapeutic areas should we apply the estimates you will provide regarding drugs, including biologics and therapeutic vaccines?

- ❒ All therapeutic areas in general
- ❒ Anti-Infective
- ❒ Cardiovascular
- ❒ Central nervous system
- ❒ Dermatology
- ❒ Endocrine
- ❒ Gastrointestinal
- ❒ Genitourinary system

- ❒ Hematology
- ❒ Immunomodulation
- ❒ Oncology
- ❒ Ophthalmology
- ❒ Pain and anesthesia
- ❒ Respiratory system

4. Please explain the basis for your selection(s) in the above question (e.g., "My expertise is in cardiology, so I am mostly familiar with those types of trials").

_____
_____
_____
_____

5. For each of the clinical phases listed, please estimate the average impact of **Mobile technologies** on the cost of a clinical trial study, the clinical trial time, and phase transition success probability, as applicable. If you do not expect **Mobile technologies** to have an impact on a particular phase or element, please leave the estimated impact at 0%.

	Clinical Trial Cost (%)	**Impact is a(n)...**	**Clinical Trial Time (%)**	**Impact is a(n)...**	**Phase Transition Success Probability (%)**	**Impact is a(n)...**
Non-Clinical Phase	____%	Increase/Decrease	____%	Increase/Decrease	____%	Increase/Decrease
Phase 1	____%	Increase/Decrease	____%	Increase/Decrease	____%	Increase/Decrease
Phase 2	____%	Increase/Decrease	____%	Increase/Decrease	____%	Increase/Decrease
Phase 3	____%	Increase/Decrease	____%	Increase/Decrease	____%	Increase/Decrease
Phase 3 - New Drugs	____%	Increase/Decrease	____%	Increase/Decrease	____%	Increase/Decrease
Phase 3 - Label Expansions	____%	Increase/Decrease	____%	Increase/Decrease	____%	Increase/Decrease
FDA NDA/BLA Phase	____%	Increase/Decrease	____%	Increase/Decrease	____%	Increase/Decrease

Phase 4	____%	Increase/Decrease	____%	Increase/Decrease	____%	Increase/Decrease

6. Please briefly explain your reasoning for the estimates you provided. You may also use the space below for additional comments, including whether or how these estimates might vary by therapeutic area.

_____
_____
_____
_____

7. Please use the space below for any additional thoughts or comments you may have for the strategies considered.

_____
_____
_____
_____

Questions 5 through 7 repeat for each strategy the respondent has selected in question 2.

PREVENTIVE VACCINES

The following questions are related to preventive vaccines.

8. We are interested in better characterizing the costs and cost drivers of a single clinical trial study for a novel preventive vaccine at a granular level, if possible. Please provide your best estimate for each of the clinical trial elements noted below. You may choose to provide a single estimate that in your opinion represents the average cost or a range (i.e., a lower and an upper bound). Please provide estimates in US Dollars ($).

		Phase 1	**Phase 2**	**Phase 3**	**Phase 4**
Per Study	Data collection, management, and analysis	_____	_____	_____	_____
	Number of IRB approvals	_____	_____	_____	_____
	Number of sites	_____	_____	_____	_____

Per Site	Site recruitment cost	_____	_____	_____	_____
	Site retention cost	_____	_____	_____	_____
	Number of patients	_____	_____	_____	_____
Per Patient	Patient recruitment cost	_____	_____	_____	_____
	Patient retention cost	_____	_____	_____	_____
	RN/CRA cost	_____	_____	_____	_____
	Physician cost	_____	_____	_____	_____
	Clinical procedure cost	_____	_____	_____	_____
	Central laboratory cost	_____	_____	_____	_____

9. Please briefly explain your reasoning for the estimates you provided. You may also use the space below for additional comments, including whether or how these estimates might vary by, for example, type of preventive vaccine.

_____
_____
_____
_____

10. We are interested in better characterizing the duration of a clinical trial study by phase for novel preventive vaccines. For each phase, please give your best estimate of the average clinical trial time, which includes the time from inception to the completion of the study report, in months.

Phase	**Average Clinical Trial Time (in months)**
Non-clinical	_____ months
Phase 1	_____ months
Phase 2	_____ months
Phase 3	_____ months
FDA BLA Phase	_____ months
Phase 4	_____ months

11. Please briefly explain your reasoning for the estimates you provided. You may also use the space below for additional comments, including whether or how these estimates might vary by, for example, type of preventive vaccine.

_____
_____
_____
_____

12. We are interested in better characterizing the phase transition success probability of a clinical trial study by phase for novel preventive vaccines. For each phase, please give your best estimate of the average likelihood a vaccine will move to the next phase.

Phase	**Average Likelihood of Success (in %)**
Non-clinical to Phase 1	_____ %
Phase 1 to Phase 2	_____ %
Phase 2 to Phase 3	_____ %
Phase 3 to FDA BLA Phase	_____ %
FDA BLA to Market	_____ %

13. Please briefly explain your reasoning for the estimates you provided. You may also use the space below for additional comments, including whether or how these estimates might vary by, for example, type of preventive vaccine.

_____
_____
_____
_____

Below is a list of strategies as available from published literature that could potentially improve clinical trial efficiency by reducing clinical trial cost, clinical trial time, or increasing the probability of phase transition success.

On the following pages, we will ask for more detailed information about the impact of each strategy on clinical trial cost, clinical trial time, and the phase transition success probability.

14. Which of the following strategies do you think could impact the clinical trial cost, clinical trial time and/or phase transition success probability of a single clinical trial?

- ❒ **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 as 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.
- ❒ **Staged approval:** Staged approval could entail granting provisional marketing approval to market a drug, complex medical device, or preventive vaccine after safety and basic efficacy have been shown, and then continuing to collect additional safety and efficacy data. This would reduce the threshold for initial approval, perhaps with a limited patient population, and then gradually expand it as more data are collected.
- ❒ **Biomarkers as surrogate endpoints:** Biomarkers as surrogate endpoints are biological indicators that may correlate with the desired clinical endpoint, for example when it would take a long time for the clinical endpoint to become evident. The strategy could entail clarifying the path to biomarker validation or encouraging collaboration between academics, public entities, and industry to develop and validate biomarkers for use as surrogate endpoints.

- ❒ **Electronic health records:** EHRs, used here as being synonymous with electronic medical records (EMRs), are digital versions of the data collected when a patient visits a healthcare provider's office. The strategy could entail encouraging sponsors to use EHRs for patient and physician recruitment or to collect clinical endpoints.
- ❒ **Patient registries:** A patient registry is an organized system that uses observational study methods to collect uniform data to evaluate specified outcomes of a disease or condition for a population. Registries include those established by a patient organization for a particular disease as well as registries that are sometimes established by the manufactured 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.
- ❒ **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.
- ❒ **CDC/NIH developing epidemiological data on disease incidence:** This strategy would entail CDC and/or NIH collecting epidemiological data on disease incidence that is tailored to developing vaccines, rather than each vaccine manufacturer collecting it individually.
- ❒ **Federally supported cGMP-compliant manufacturing facilities:** This strategy would entail providing additional funding or other support to help increase the number/capacity of cGMP-compliant manufacturing facilities that can produce batches of vaccines for use in clinical trial studies.

15. For each of the clinical phases listed, please estimate the average impact of **Mobile technologies** on the cost of a clinical trial study, the clinical trial time, and phase transition success probability, as applicable. If you do not expect **Mobile technologies** to have an impact on a particular phase or element, please leave the estimated impact at 0%.

	Clinical Trial Cost (%)	**Impact is a(n)...**	**Clinical Trial Time (%)**	**Impact is a(n)...**	**Phase Transition Success Probability (%)**	**Impact is a(n)...**

Non-Clinical Phase	____%	Increase/Decrease	____%	Increase/Decrease	____%	Increase/Decrease
Phase 1	____%	Increase/Decrease	____%	Increase/Decrease	____%	Increase/Decrease
Phase 2	____%	Increase/Decrease	____%	Increase/Decrease	____%	Increase/Decrease
Phase 3	____%	Increase/Decrease	____%	Increase/Decrease	____%	Increase/Decrease
Phase 3 - New Drugs	____%	Increase/Decrease	____%	Increase/Decrease	____%	Increase/Decrease
Phase 3 - Label Expansions	____%	Increase/Decrease	____%	Increase/Decrease	____%	Increase/Decrease
FDA NDA/BLA Phase	____%	Increase/Decrease	____%	Increase/Decrease	____%	Increase/Decrease
Phase 4	____%	Increase/Decrease	____%	Increase/Decrease	____%	Increase/Decrease

16. Please briefly explain your reasoning for the estimates you provided. You may also use the space below for additional comments, including whether or how these estimates might vary by therapeutic area.

_____
_____
_____
_____

17. Please use the space below for any additional thoughts or comments you may have for the strategies considered.

_____
_____
_____
_____

Questions 15 through 17 repeat for each strategy the respondent has selected in question 14.

COMPLEX MEDICAL DEVICE QUESTIONS

The following questions are related to complex medical devices.

Please recall that by "complex medical device," we are referring to those devices that require FDA premarket approval (PMA) ONLY. Those medical devices subject to the de novo and 510(k) route are not in scope for this questionnaire.

18. We are interested in better characterizing the costs of clinical trials for novel complex medical devices (i.e., devices that require FDA premarket approval) at a granular level, if possible. Please provide your best estimate for each of the clinical trial elements noted below. You may choose to provide a single estimate that in your opinion represents the average or a range (e.g., a lower and an upper bound). Please provide estimates in US Dollars ($).

		Pilot Study Phase	**Pivotal Study Phase**	**Post-approval Study Phase**
Per Study	Data collection, management, and analysis	_____	_____	_____
	Number of IRB approvals	_____	_____	_____
	Number of sites	_____	_____	_____
Per Site	Site recruitment cost	_____	_____	_____
	Site retention cost	_____	_____	_____
	Number of patients	_____	_____	_____
Per Patient	Patient recruitment cost	_____	_____	_____
	Patient retention cost	_____	_____	_____
	RN/CRA cost	_____	_____	_____
	Physician cost	_____	_____	_____
	Clinical procedure cost	_____	_____	_____
	Central laboratory cost	_____	_____	_____

19. Please briefly explain your reasoning for the estimates you provided. You may also use the space below for additional comments, including whether or how these estimates might vary by, for example, type of complex medical device.

_____
_____
_____
_____

20. We are interested in better characterizing the total duration of a clinical trial study by phase for novel complex medical devices. For each phase, please give your best estimate of the average clinical trial time, which includes time from inception to the completion of the study report, in months.

Phase	Average Clinical Trial Time (in months)
Non-clinical Phase	_____ months
Pilot Study	_____ months
Pivotal Study Phase	_____ months
FDA PMA Phase	_____ months
Post-approval Study Phase	_____ months

21. Please briefly explain your reasoning for the estimates you provided. You may also use the space below for additional comments, including whether or how these estimates might vary by, for example, type of complex medical device.

_____
_____
_____
_____

22. We are interested in better characterizing the phase transition success probability of a clinical trial study by phase for novel complex medical devices. For each phase, please give your best estimate of the average likelihood a complex medical device will move to the next phase.

Phase	Average Likelihood of Success (in %)
Non-clinical to Pilot Phase	_____ %
Pilot Phase to Pivotal Phase	_____ %
Pivotal Phase to FDA PMA Phase	_____ %
FDA PMA Phase to Market	_____ %

23. Please briefly explain your reasoning for the estimates you provided. You may also use the space below for additional comments, including whether or how these estimates might vary by, for example, type of complex medical device.

_____
_____

Below is a list of strategies as available from published literature that could potentially improve clinical trial efficiency by reducing clinical trial cost, clinical trial time, or increasing the probability of phase transition success.

On the following pages, we will ask for more detailed information about the impact of each strategy on clinical trial cost, clinical trial time, and the phase transition success probability.

24. Which of the following strategies do you think could impact the clinical trial cost, clinical trial time and/or phase transition success probability of a single clinical trial?

- ❒ **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 as 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.
- ❒ **Staged approval:** Staged approval could entail granting provisional marketing approval to market a drug, complex medical device, or preventive vaccine after safety and basic efficacy have been shown, and then continuing to collect additional safety and efficacy data. This would reduce the threshold for initial approval, perhaps with a limited patient population, and then gradually expand it as more data are collected.

- ❒ **Biomarkers as surrogate endpoints:** Biomarkers as surrogate endpoints are biological indicators that may correlate with the desired clinical endpoint, for example when it would take a long time for the clinical endpoint to become evident. The strategy could entail clarifying the path to biomarker validation or encouraging collaboration between academics, public entities, and industry to develop and validate biomarkers for use as surrogate endpoints.
- ❒ **Electronic health records:** EHRs, used here as being synonymous with electronic medical records (EMRs), are digital versions of the data collected when a patient visits a healthcare provider's office. The strategy could entail encouraging sponsors to use EHRs for patient and physician recruitment or to collect clinical endpoints.
- ❒ **Patient registries:** A patient registry is an organized system that uses observational study methods to collect uniform data to evaluate specified outcomes of a disease or condition for a population. Registries include those established by a patient organization for a particular disease as well as registries that are sometimes established by the manufactured 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.
- ❒ **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.
- ❒ **Encouraging the use of centralized IRBs:** A centralized Institutional Review Board is a single IRB of record for all clinical trial sites in a multi-center trial, which would remove the need to obtain approvals from multiple local IRBs. The strategy could entail creating guidance or other educational material and encouraging local IRBs not to require local IRB approval.

25. For each of the clinical phases listed, please estimate the average impact of **Mobile technologies** on the cost of a clinical trial study, the clinical trial time, and phase transition success probability, as applicable. If you do not expect **Mobile technologies** to have an impact on a particular phase or element, please leave the estimated impact at 0%.

Clinical Trial	Impact is a(n)...	Clinical Trial Time (%)	Impact is a(n)...	Phase Transition Success	Impact is a(n)...

	Cost (%)				**Probability (%)**	
Non-Clinical Phase	____%	Increase/Decrease	____%	Increase/Decrease	____%	Increase/Decrease
Feasibility Study Phase	____%	Increase/Decrease	____%	Increase/Decrease	____%	Increase/Decrease
Pivotal Study Phase	____%	Increase/Decrease	____%	Increase/Decrease	____%	Increase/Decrease
FDA PMA Phase	____%	Increase/Decrease	____%	Increase/Decrease	____%	Increase/Decrease
Post-approval Phase	____%	Increase/Decrease	____%	Increase/Decrease	____%	Increase/Decrease

26. Please briefly explain your reasoning for the estimates you provided. You may also use the space below for additional comments, including whether or how these estimates might vary by therapeutic area.

_____
_____
_____
_____

27. Please use the space below for any additional thoughts or comments you may have for the strategies considered.

_____
_____
_____
_____

Questions 25 through 27 repeat for each strategy the respondent has selected in question 24.

END

Thank you for responding to our questions.

APPENDIX B – DETAILED EXPERT ESTIMATES FOR DRUGS, BY THERAPEUTIC AREA

Table 7. 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.