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Productivity Trends in Cardiovascular Clinical Trials

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Abstract

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In order to evaluate and characterize clinical trial cost trends between 1999 and 2012, we retrospectively analyzed existing NIH-funded interventional cardiovascular clinical trials on publicly available NIH and clinicaltrials.gov databases. The primary aims of this study were to characterize trial productivity, or outputs per unit of input, and to delineate trends in costs per patient from 1999 to 2012. Study design and data collection included clinical trial analysis with the following question in mind: Has the cost of conducting cardiovascular clinical trials decreased over time? Study results suggest rejection of the initial hypothesis that costs per patient have declined over time, indicating that costs per patient have increased at roughly 15% per year. Consequently, results suggest information technology has not reduced the cost of conducting clinical trials. In addition to outlining several characteristics that may contribute to increasing costs per patient, this research also provides further data on publicly funded clinical trials and contributes to the current body of knowledge on productivity. Results of increasing costs per patient can be used to inform decisions about healthcare, research trial funding, and study design. Further research from both the public and private sector on patient enrollment, trial length, and conditions studied is necessary.

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INTRODUCTION

Foreword: Clinical Trial Significance

Randomized clinical trials provide support for robust research and serve as a gold standard in the evaluation of safety and potential efficacy for treatment drugs, devices, and strategies (Nallamothu et al., 2008). The importance in investigating clinical trial costs and efficiency is clear because funds appropriated for scientific inquiry are fundamentally limited. Because funds from both the public and private sector are spent on clinical trials, it is as important as ever to investigate trial costs, optimize how research dollars are used, and maximize research on good trials. This particular study investigates a particular branch of clinical trials, cardiovascular clinical trials, but is by no means exclusive to this subcategory in it's objective of characterizing trial cost trends. In this study, pinpointing cardiovascular disease narrows down research parameters and allows for a more focused investigation, but is not meant to detract from the more prominent premise that it is important to study the costs of all clinical trials.

Burden of Disease and Risk Factors:

According to the World Health Organization (WHO), cardiovascular diseases (CVD), defined as diseases of the heart and blood vessels, are the number one cause of death globally, accounting for 31% of all deaths (WHO, 2011). This class of diseases, including conditions like heart attack and stroke, can be largely attributed to coronary artery disease (CAD) and the underlying atherosclerotic processes that lead to plaque buildup, eventual obstruction of blood flow, and impending heart failure (CDC, 2015). Though disease pathogenesis is complex and can be chronic, acute, or recurrent, key risk factors for developing CVDs include hypertension,

hypercholesterolemia, and smoking (Fryar, 2012). Unfortunately, 47% of Americans have at least one of these three risk factors (Fryar, 2012).

Though some risk factors like family history and age cannot be controlled, behavioral and biological factors work hand in hand as underlying contributors to the heightened burden of cardiovascular disease. Behavioral influences like high fat diets and sedentary lifestyles have shifted disease patterns from infectious diseases to non-communicable diseases, contributing to the burden of CVD (Yusuf, 2001). Downstream biological effects of cardiovascular risk also include several abnormal responses in both macro- and microvasculature like oxidization of unhealthy low-density lipoprotein cholesterol (LDL) and chronic inflammation, both of which contribute to the formation of atherosclerotic plaque (Dokken, 2008). This tension and trauma can lead to increased hypertension and coagulation, often causing blood vessels to burst and restrict blood supply to the heart and brain, triggering neuronal death and brain damage, disability, or death (National Institute of Neurological Disorders and Stroke, 2016).

Addressing Cardiovascular Disease

In response to this clear burden, the scientific and medical community have been working for decades to better understand and address CVDs. The National Heart Institute (now known as the National Heart, Lung, and Blood Institute) was one of the first pioneers in CVD research, directing comprehensive multigenerational studies like the Framingham Study, that continue to identify CVD risk factors and develop diagnostic tools (Mahmood, Levy, Vasan, & Wang, 2013). Such research, coupled with additional discoveries in technology and advancements in cardiovascular drug therapy, have contributed to the improved prevention, diagnosis, and treatment of CVDs (Weisfeldt & Zieman, 2007).

Beginning in the 1970s, a two-pronged approach involving pharmaceutical drugs and complex, costly procedures sparked a dramatic 50% age-adjusted decline in mortality attributed to CVDs over the past thirty-five years (Weisfeldt & Zieman, 2007). Drug interventions targeting enzymes, receptors, and channels allow for more effective ways to combat CVD morbidity and mortality. Lipid-lowering statins reduce inflammation and oxidative stress by disrupting an enzyme that forms LDL, antihypertensive agents promote blood pressure control by acting on enzymes, channels, and receptors, and thrombotic agents like aspirin and warfarin dissolve existing clots and prevent new ones from forming (Weisfeldt & Zieman, 2007). These interventions provide life-saving solutions to CVD patients suffering from a wide range of conditions, but as CVD treatment types evolve in complexity, a series of questions regarding treatment quality, efficacy, and effectiveness naturally emerge. As per existing literature, efficacy research investigates whether a study is successful at observing an intervention under ideal conditions, whereas effectiveness research investigates the effects of an intervention on clinical practice (Singal, Higgins, & Waljee, 2014).

The need for data-driven answers can be in part answered by randomized clinical trials. By including economic evaluation, budget impacts, and cost characteristics, clinical trials can be used to guide scientific inquiry in ways that provide policymakers with relevant and applicable data (Baltussen et al., 1999). In addition to death and disability, relevant fluctuations in the cost of successful CVD clinical trials are major contributors to the CVD burden of disease and can provide meaningful insight into further research needs and subsequent policy implications. In accordance with this concept, identifying trends in clinical trial costs, and more specifically monetary expenditures (spending) per clinical trial patient, is a primary focal point of this study. Understanding the aforementioned clinical trial features, such as classifications and funding, can provide additional support in the pursuit to characterize CVD clinical trials.

STATEMENT OF THE PROBLEM

Cardiovascular Disability and Cost Concerns:

Amidst analyzing the burden of CVDs, a primary motivator for this study includes delineating the cost of conducting CVD clinical trials. In order to quantify the true cost of heart disease and stroke in the United States though, one must look beyond mortality rates, at costs related to health care expenditures. The estimated sum costs of CVDs was estimated at $475.3 billion in 2009. According to a statistical update from the American Heart Association (AHA), this sum includes: $313.8 billion in direct medical expenses; $39.1 billion in lost productivity due to sickness or disability; and $122.4 billion in lost productivity due to premature death (Lloyd-Jones, 2009).

In 2006, United States health care spending was $2.1 trillion, and health care contributed to 16% of the gross domestic product (GDP) (Catlin et al., 2008). That same year, spending on CVDs represented approximately 17% of all national health expenditures (Trogdon et al., 2007). Assuming an increasingly aging and overweight population, suboptimal preventive measures, and no policy changes over time, the costs of CVDs are predicted to exceed $1 trillion by 2030, including $818.1 billion in direct costs and $275.8 billion in indirect costs calculated in real 2008 dollars (Heidenreich et al., 2011). These rising healthcare costs are unsustainable and it is clear that cardiovascular health comes with a hefty price tag that must be addressed when seeking to efficiently and effectively alleviate the burden of CVDs. Key potential arguments for underlying motivators of increased healthcare costs also include cost associated with technological innovation (like the costs of more frequent coronary bypass surgeries and angioplasties), excessive administrative expenditure related to poorly integrated health financing and delivery

systems, and inadequate cost-containment regulations that prevent the use of expenditure caps and budgets (Bodenheimer, 2005).

CVD Trial Drivers: Technological Devices, Procedures, and Diagnostics

Though the United States is an innovative player in the global healthcare market, there is great discussion and controversy regarding the value of increased health care spending and its relation to technological innovation. Approved medical technology is a major industry that contributes towards increased clinical spending. This sector is closely linked to advances in diagnostic testing, drug treatments, medical devices, and delivery procedures, many of which claim to save lives and reduce mortality rates by up to 21%, as in the case of acute myocardial infarction (Rothberg et al., 2010). However, not all technologies are undoubtedly beneficial. Certain medical advancements are beneficial because they offer treatments to otherwise untreatable conditions, while others can be marginally beneficial at an excessive cost, and some offer no additional benefits beyond the existing standard of care (Orszag & Ellis, 2007). For example, Redberg provides an overview of cardiac computed tomography angiography (CTA) and calls for an evidence-based review of such new technology due to high costs, rapid implementation, and an often-lacking foundation of evidence prior to adoption (2007). As a diagnostic tool, rather than a life-saving procedure, CTA scanning improves image resolution but imparts little to no benefit to the patient (Redberg, 2007).

Though new technology may require further research prior to widespread use, technological innovation also permits novel research methods with which to conduct further investigation. Starting in the early 1960's, the development of technological procedures like coronary angiography, cardiac catheterization, intracoronary stenting, echocardiography, emergency defibrillation, implantation of intracardiac defibrillators (ICDs), high resolution computed tomography (CT) scanning, and cardiac transplants have contributed to a 50% decline in mortality attributable to CVDs (Weisfeldt & Zieman, 2007). The advent of big data, electronic

health records (EHRs), and comprehensive patient registries, have also prompted researchers to investigate the use of clinically-founded data as a means to conduct extensive retrospective studies for determining interventional efficacy (Longhurst et al., 2014). New technology therefore holds the potential to serve as a catalyst for novel research methods and multidisciplinary innovation that includes cardiovascular health.

When considering changes in technology concerning the treatment of heart attacks, treatment options include medical management through thrombolysis and supportive care, surgical interventions like bypass surgery and angioplasty, and preventive drug therapies (Cutler & McClellan, 2001). Between 1984 and 1998, the total dollar amount spent on heart attack patients increased by 3.4% and the dollar amount spent per heart attack increased by roughly $10,000 per incident, or 4.2% increase per year (Cutler & McClellan, 2001). Remarkably, 45% of the cost increases during this period are due to technologies applied to more patients over time in hopes of reducing complications and improving outcomes (Cutler & McClellan, 2001). More specifically, the primary technology-related factor responsible for this increased cost is not the development of new therapies, but instead relates to extending existing and often costly interventions to a larger patient population (Cutler & McClellan, 2001). According to Cutler & McClellan, technological change is costly, but it is also beneficial in that it increases QOL, earning potential, work productivity, and life expectancy (2001). They also argue that due to the value of such benefits, the net benefit of technological change and adaption of post clinical trial heart attack management is justifiable, estimating that every $1 spent yields a $7 benefit (Cutler and McClellan, 2001).

On the other hand, healthcare technology changes may also have several unintended downstream effects that can impact clinical research and medical treatment. The lucrative field

of information technology (IT) and medical equipment may create monetary challenges for hospitals and hospital-based health systems. When linked with calls for increased safety, quality, and performance, hospital planning can be disrupted by the demand for the most up-to-date technology (Coye & Kell, 2006). Factors for planning technology in a hospital, including locus of decision making, competition, and physician preference, can all play a role in the purchase of new technology, IT, or major medical equipment, a costly endeavor that accounted for half of all hospital capital spending in 2001 (Coye & Kell, 2006). Therefore, innovative approaches in technological prevention and treatment ideally require smooth implementation coupled with full extraction of value. This could, in part, be addressed by technologically streamlining healthcare information sharing. Expanded use of electronic medical records (EMRs) and the promotion of fully standardized healthcare information exchange and interoperability (HIEI) between healthcare providers has the potential to address excessive administrative expenses, and save $77.8 billion per year (Walker et al., 2005). However, technology-hungry health consumers and providers must bear in mind the cost-effectiveness of technology because most consequent savings are dwarfed by sizable, extremely costly, and occasionally beneficial technological advancements like robotic surgery and three-dimensional echocardiography (Kumar, 2011). These cost-relevant IT approaches and potential savings can be extended clinical trials.

CVD Trial Drivers: Computers, Information Technology (IT), and Switchover Disruptions

The effects of technology are also important beyond reasons of monetary cost, such that computers and IT have been shown to increase work productivity, or the efficiency with which inputs are transformed into outputs. For example, a survey sampling from 1987 to 1993 indicates a 3% increase in the spread of personal computer or computer terminal use in the workplace, and an overall increase in productivity attributed to IT in French industries involving food products, consumer goods, commerce, banking, and insurance (Greenan & Mairesse, 1996). In addition, computers and IT that collect information, such as on-board computers (OBC) in the trucking industry, have been shown to increase capacity utilization and productivity by providing real-time information, facilitating communication, and impacting resource allocation decisions (Hubbard, 2001).

Thus, IT has facilitated productivity growth across industries and countries, yet costly barriers to adopting productivity-enhancing practices still exist. Holmes, Levine, and Schmitz argue that fully assessing productivity involves widespread and durative implementation of new technology in order to account for challenges due to switchover disruptions, defined as temporary technology adoption costs (2008). They propose that especially in competitive environments, complications due to technology installation, acclimatization, and coordination can lead to suboptimal productivity and high costs of innovation.

Computers and IT may also impact the health industry considering the increasing technological interventions described. More specifically, such technology may affect interventional cardiovascular clinical trial productivity, or the efficiency with which trial costs are converted to outputs. An example of such an effect is demonstrated in the case of neurosurgical endovascular techniques and functional technologies like deep brain stimulation

contributing to more scientific publications and increased productivity (Hauptman et al., 2011). In this study, outputs include patients studied in completed, interventional cardiovascular trials that yield results.

CVD Trial Drivers: Drug Development and Drug Therapies

A hallmark, but provocative, study by DiMasi, Hansen, & Grabowski estimated the general cost of pharmaceutical drug innovation, as measured by the average cost associated with successful approval of a pharmaceutical drug, at $802 million in 2000 dollars (2003). Drug trials are critical for ensuring safety and efficacy, but there are many discrepancies and issues associated with the arduous process (Nallamothu et al., 2008). FDA regulation is strict and comprehensive studies can take up to 20 years to complete, though many trials may terminate early, leading to incredibly high sunk costs (Dickson & Gagnon, 2004). The search to offset and recover these sunken research and development (R&D) investments leads to high drug prices. Most interventional clinical trials fall under the category of interventional drug trials, and are subject to the similar factors promoting an increase in costs (Roumiantseva et al., 2013).

There are several differing perspectives on clinical research and development cost trends, particularly regarding drug development. One of these includes the view that drug costs are justifiably high due to elevated research and development expenditures (Bollyky, Cockburn, & Berndt, 2010). Increased costs are related to increased research complexity, the recent increase in the study of chronic illness, cumulative increases in trial regulations, increased study globalization, commercial practices, and the need to maximize profitable patent life (Bollyky et al., 2010). Drug development innovations have allowed for significant improvements in the translation of clinical research to medical treatments. For example, the widespread use of statins (HMG-CoA reductase inhibitors that block the enzyme responsible in creating cholesterol) in 2008 was shown to reduce low-density lipoprotein (LDL) cholesterol by 18.8%, lead to 40,000 fewer deaths, and prevent 82,000 hospitalizations for heart attacks and stroke (Grabowski et al., 2012).

Scope: Why do we care? Cardiovascular Clinical Trials in Depth:

Finding safe and effective treatment drugs, devices, and strategies for CVDs involves the consideration of diverse expenditures. Clinical trials may provide cost-efficient and effective solutions to these problems, as well as support for decision-making in clinical and health policy (Tunis, Stryer, & Clancy, 2003). However, clinical trials in the U.S. are becoming more expensive, and factors like increased international research, NIH funding, emerging technologies, tax environments, and FDA regulatory approvals are changing the landscape of clinical trials. (DeVol et al., 2011). As an important step in both innovation and commercialization of medical products, clinical trials represent a considerable portion of the economy. As of 2011, the United States hosted 50.9% of all clinical trials in the world and was responsible for 57% of new chemical entities (NCEs) produced (DeVol et al., 2011). Additionally, the number of cardiovascular research publications per year has also increased over the past decades, from just fewer than 2,000 publications per year in 1991 to almost 8,000 in 2013 (Kapoor et al., 2015). Due to this increase in volume, it is benefit to understand clinical trial cost trends and underlying cost drivers.

Scope:

Though it is clear that America's existent CVD epidemic presents a significant public health challenge, there is considerable uncertainty in regards to CVD clinical trial productivity. Because CVD is prevalent and its burden costly, this study aims to delineate trends in cardiovascular clinical trial costs, which are assumed to affect the actual price of cardiovascular therapies. Such knowledge can inform and impact future policy decisions that seek to maximize relevant, valuable, and effective research. In this study, funding allocated by the National Institutes of Health (NIH), a division of the U.S. Department of Health and Human Services, is of key importance, because among several other types of clinical trials, the NIH supports cardiovascular clinical trial research that conceivably holds the potential to resolve many of the ailments plaguing cardiovascular health.

METHODOLOGY

The primary goal of this study was to describe trends in cardiovascular clinical trial spending in order to better characterize changes in productivity and efficiency. However, to accomplish this, it was necessary to identify and isolate variables that could impact cost calculation. With this in mind, eligibility criteria included several restrictions.

Selection Criteria:

NIH funded trials were primarily used due to availability of cost and enrollment data. Additionally, due to previous use of public sector information to increase economic growth and effectiveness, publicly available data was used to safeguard data transparency (Jaatinen, 2016). Previous research has also utilized clinical trial searches to investigate productivity (Prasad & Goldstein, 2014). The data used in this study contain information collected from Clinicaltrials.gov and the National Institutes of Health RePORTER site. Search terms included separate searches for "Cardiovascular," "Stroke," and "Heart" yielding hundreds of search results.

Selecting "Interventional Studies" from the ClinicalTrials.gov study-type selection in advanced search automatically served as a first screen for the trials. In addition, to prevent complications from terminated or incomplete studies, trials were further screened such that recruitment and result types were limited to completed, closed studies with results. Trials with unknown status were excluded, and funder type was limited to NIH and other U.S. federal agencies.

Why Interventional Trials?

According to the World Health Organization (WHO), research interventions encompass the use drugs, biological products, procedures, devices, surgeries, diagnostics, and prevention strategies (2016). Interventional study designs are often prospective and directly evaluate the effect of an intervention on disease, whereas epidemiological studies are often retrospective and involve observing experimental variables and outcomes (Thiese, 2014). Both have respective limitations in that observational and retrospective studies are subject to recall bias, while prospective and interventional studies require several studies to establish causation and can be expensive (Thiese, 2014). Previous studies also indicate that among government-sponsored trials, 64% of all trials are interventional, and 36% are observational (Roumiantseva et al., 2013). Due to the high government sponsorship of interventional trials, as well as the high cost implications, and biological nature of CVD clinical research, analysis was restricted to interventional CVD clinical trials. Intervention type was also recorded to allow for identification and analysis of potential cost drivers.

Primary monetary grant information was recorded based on the clinical trial collaborator, who oversees the clinical study, as opposed to sponsor, who provides funding, design, implementation, analysis, and reporting support (U.S. National Library of Medicine, 2015). As a redundancy, careful manual screening excluded trials that included private collaborators that were not excluded automatically by the search engine. In addition, trials funded by government sources that could not be traced due to the limited resources of this study, including those funded by the Department of Defense (DOD) or the VA Office of Research and Development, were also excluded. This study mainly investigated government funded trials that were supported by NIH divisions, namely the NIH like the National Heart, Lung, and Blood Institute (NHLBI) and the

National Institute of Neurological Disorders and Stroke (NINDS). Through these selection criteria, clinical trial cost could be traced more directly.

Why Federally Funded Trials?

According to a detailed analysis of clinicaltrials.gov trials, supported in part by the Department of Veteran Affairs, there are several key differences between government-sponsored and industry-sponsored clinical trials (Roumiantseva et al., 2013). Among government-only sponsored trials, 64% were interventional (and 36% were observational), whereas among industry-only sponsored trials, most trials (90%) were interventional (Roumiantseva et al., 2013). In both government- and industry-sponsored interventional trials, the most frequent intervention type was drug trials, with 81% for industry-only, and 52% for government-only sponsored interventional trials belonging to this category (Roumiantseva et al., 2013). Due to previous research literature indicating that clinical trials funded by pharmaceutical companies may result in design and outcome bias as a result of funding pressures, this study is limited to government-only funded trials for the purposes of access and transparency, and to limit potential industry bias and tracing challenges associated with industry-funding data (Lexchin et al., 2003).

Variables Collected:

Forty-four trials were collected in this study. Data collection included the following variables: The Trial Title; Clinicaltrials.gov Identifier; First Received Date (the date on which summary clinical study protocol information was first submitted to the ClinicalTrials.gov registry); Study Start Date; Study Completion Date; Sponsors; Collaborators; Study Type (Interventional); Condition; Intervention; Total Number of Patients; Mean Patients Age.

Tracing Data from Clinicaltrials.gov to NIH RePORTER:

Subsequent to collection of the described variables, each clinicaltrials.gov identifier was input into the NIH RePORTER website to access funding data. Fiscal year was set to include all years (from 1992 to 2016). Activity Code, Fiscal Year, and Fiscal Year Total Cost by IC (Institute and Center) were collected from NIH RePORTER trial searches. NCT tracing from clinicaltrials.gov to the NIH RePORTER allowed for matching of selected trials with with fiscal data from the NIH. Aggregation of data from both sources allowed for trial characterization in addition to grant funding description.

Variable Descriptions:

Collaborator and Sponsor were recorded in order to provide information on funders and organizations involved. Private industry collaborators were excluded.

Temporal information included first received date, study start date, and study completion date. The first received date marks receipt of study information by the ClinicalTrials.gov registry, while the study start and end date signify study duration from initial patient enrollment to final data collection (U.S. National Library of Medicine, 2015). For this study, the first

received date spans from 1999 to 2012. Study duration (in months) was calculated by subtracting study completion date from study start date.

From the "Study Results" section of the clinicaltrials.gov study record details, total number of trial patients and the total mean age were recorded from the baseline measures tab. In addition, conditions and interventions were recorded from the purpose tab.

Conditions were categorized as either "acute" or "non-acute" following an analysis of 53 total conditions. Of the 53 conditions included in this study, 21 were acute based on disease onset. Non-acute conditions are assumed to be chronic. Differentiation was based on previous literature on heard disease, indicating a classification scheme based on disease onset and urgency; acute conditions show rapid onset and often require immediate medical care, whereas non-acute conditions involve the need for continued care of developing and often worsening conditions that persist for at least a year after onset of an initial acute event (McMurray et al., 2012). CVD classifications can include acute conditions such as strokes, myocardial infarctions, and atrial fibrillations, as well as chronic conditions such as CAD, peripheral artery disease, and hypertension. Though other CVD classifications (such as congenital heart disease) exist, the scope of this study is limited to chronic and acute in order to maintain research simplicity and a binary descriptive investigation. The two categories innately demand differential clinical trial requirements based on the nature of the disease manifestation. For example, acute CVDs such as sudden heart attacks elicit a critical need for rapid response, emergency procedures, and expedient information sharing platforms where delayed access can lead to increased myocardial damage and mortality (Luepker et al., 2000). This need is also apparent in strokes and other vascular conditions where medical reaction time and time-to-treatment of vascular rupture is

closely linked with prognosis and outcomes (Saver, 2010). This study examines CVD classifications to the extent that different disease categories may distinctively impact cost.

Interventional types were classified as behavioral (Behav), biological, device, drug, procedure (Proc), and other, signifying the type of intervention used to test cardiovascular trials. These intervention classifications were based on the collected variables, and included examples such as statin drug therapy, interracial angioplasty, and dietary supplementation. Within these inclusions, combinations of interventions were documented to provide more specific data. For example, some intervention types included both drugs and procedures, and were correspondingly recorded as an intervention that included both subtypes. Intervention types included: Drug (n=23); Drug+Proc (n=1); Drug+Behav (n=1); Drug+Diet (n=1); Drug+Other (n=4); Drug+Proc+Behav (n=1); Drug+Proc+Other (n=1); Biological (n=5); Proc+Device (n=1); Device (n=2); Device+Other (n=2) and Other (n=2). Cost data was collected from searches of each trial's clinical trial identifier from all fiscal years on the NIH RePORTER query form.

NIH Activity codes were recorded to differentiate between the wide variety of research-related programs. The codes involved in this study include those corresponding to research grants (R-series), Career Development Awards (K-series), and Research Project Cooperative Agreements. Among the cooperative agreements, U01 coded trials were used because these "support discrete, specified, circumscribed projects to be performed by investigator(s) in an area representing their specific interests and competencies" (National Institutes of Health, 2016).

Further data exclusions were made to account for studies that met clinicaltrials.gov selection criteria but failed to yield appropriate fiscal results. Some searches resulted in fiscal data that spanned across several institutes, locations, and organizations, as was the case with activity code categories that included broad cooperative agreements (P01) and program projects.

Specified activity codes in the analysis included:K23 (n=1), KL2 (n=1), P50 (n=1), R01 (n=17), R21 (n=5), R44 (n=3), RC2 (n=1), U01 (n=14), and U10 (n=1), though roughly 70% of the trials were associated with activity code categories related to research projects (R01) and discrete cooperative agreements (u01). Aside from this discrete research type, one study was coded as a P50 Grant, used to "support any part of the full range of research and development from very basic to clinical" (National Institutes of Health, 2016). This study was included due to clearly and concisely presented funding data, despite its broad variety of supported research.

Funding institutes and centers were recorded from the NIH RePORTER site to provide an extra layer of transparency beyond the clinicaltrials.gov site. Funding IC's in this study include: Office of the Director (OD); National Center for Complementary and Alternative Medicine (NCCAM); National Center on Minority Health Development (NCMHD); National Center for Research Resources (NCRR); National Heart, Lung, and Blood Institute (NHLBI); National Institute on Aging (NIA); National Institute of Child Health and Human Development (NICHD); National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK); National Institute of Neurological Disorders and Stroke (NINDS); National Institute of Nursing Research (NINR). Grant awards (termed costs) for each year were recorded, often with more than one IC contributor per year.

Calculation and Graphical Design:

Individual yearly grant awards were summed to compile a total cost per trial dollar amount. Dividing total trial cost by the number of trial patients generated total cost per patient (or grant spending per patient). This key measure provides data on how much funding is being

used per study patient and can be used to interpret trends in cardiovascular clinical trial productivity.

For each intervention, the following data were recorded and/or calculated: Number of Studies (frequency); Average Study Duration; Average Age; Total # of Patients; Average # of Patients (number of patients/number trials that correspond with that intervention); Total Cost for each intervention type; Average Cost for each intervention type (Total cost for a particular intervention type/number trials that correspond with that intervention); Total Cost per Patient. Analogous data categories were selected to record and/or calculate data from all studies in a particular year.

Clinical trial characteristics between 1999 and 2012 were analyzed based on Year Received, charting trends for Cost/Patient, Total Cost, Number of Patients, Study Duration, and Average Age. Using Microsoft Excel, trend lines were then plotted, and R^2 were documented, to aid in interpretation and evaluation of cost trends. Natural log of cost per patient was used to correct for the presence of outliers and to stabilizing the variance in the data.

Outliers:

Two outlier trials include trial NCT00000479 (year 1999) and NCT01442129 (year 2011) due to disproportionate trial patient size in relation to cost. Trial NCT00000479 included 39,876 patients (roughly 67% of the 59,182 total patients for all 44 trials), and trial NCT01442129 included only 30 patients for a trial that cost over $44 million, bringing the trial's cost/patient to $1,484,370/patient. This figure is 255% that of the next most expensive trial/patient at $582,967.80. Due to their capacity to skew the data, these outliers were excluded from graphs and calculations that presented data with the above trials. Outliers were excluded if they exceeded 5.5 times the interquartile range. Using these outlier criteria excludes trials with more

than 2,270 patients, and trials costing more than $400,000 per patient. A minimum grant amount of $1 was also excluded. Appropriate notations were presented accordingly graphs and tables.

Data Analysis:

A least squares regression was conducted in order to test correlations and determine whether there is a statistically significant relationship between ln (Cost/patient), Year 1st received, and the number of patients enrolled.

RESULT: SUMMARY TABLES AND FIGURES

Forty-four cardiovascular clinical trials met selection criteria. Total spending of these trials between 1999 and 2012, as measured by the collective NIH grant funding received, was $496 billion, and was composed of 293 individual grants (Table 1). Average grant size was $1.7 million, with largest grants peaking at $10.7 million and smallest dipping to $7,460. On average, there were greater than six individual grants per clinical trial.

Table 1.

NIH Grant Details	
Total Grant Count	293
Total Grant Sum	$496,382,697
Average Grant Amount (/293)	$1,694,138
Min Grant Amount	$7,460
Max Grant Amount	$10,731,771

In this sample, the NHLBI is a major contributor (65.89%) for NIH-funded cardiovascular trials, as is the NINDS, contributing 28.34%. The studies include funding sources ranging across 10 of the 27 NIH ICs, with over 94% of total funding originating from the National Heart, Lung, and Blood Institute (NHLBI) and the National Institute of Neurological Disorders and Stroke (NINDS).

Table 2:

NIH IC's	Grant amounts	Grant amount %
NHLBI	$327,065,091	65.89
NINDS	$140,656,229	28.34
NCCAM	$15,782,405	18
NCMHD	$300,000	3.0.06
NIDDK	$5,262,500	1.06
OD	$2,278,615	0.46
NIA	$2,052,401	0.41
NINR	$2,055,145	0.41
NICHD	$884,311	0.18
NCRR	$46,000	0.01
Total	$496,382,697	100.00

The frequency of studies included comprised a maximum of 11 (25%) studies per year in 2009, and a low of zero studies in 2001 (Table 3). In addition, Table 3 presents average duration of trials based on the year they were first received, total number of yearly patients, total yearly costs of all studies, and total spending per patient for each given year.

Table 3:

Year 1st Received	Trial Freq.	Avg Duration (months)	Total # of Patients	Total Cost of All Studies	Total Spending/ Total Patients
1999	1	149	39876	$13,044,220	$327
2000	2	121.5	4569	$69,719,895	$15,259
2001	0	0	0	$0	$0
2002	3	112.33	4402	$55,545,266	$12,618
2003	2	84	3716	$79,120,115	$21,292
2004	2	69	1705	$27,705,783	$16,250
2005	4	77	723	$12,193,670	$16,865
2006	4	64	356	$7,589,896	$21,320
2007	5	52.6	1887	$65,919,358	$34,933
2008	4	55.5	697	$25,684,909	$36,851
2009	11	41.82	774	$70,366,386	$90,913
2010	1	34	360	$19,754,513	$54,874
2011	3	14.33	86	$46,388,335	$539,399
2012	2	22.5	31	$3,350,351	$108,076
Total	44		59182	$496,382,697	

In the binary split between interventional trials addressing acute and non-acute conditions, those involving acute conditions account for 62% of the time, 57% of costs, 57% of the number of trials, and 89% of the patients involved (Table 4). Although interventional trials concerning acute conditions are more expensive on the aggregate level, they are only 1/6th ($5,300) as expensive per patient as compared to interventional trials concerning chronic conditions ($32,000).

The majority of clinical trials involve drug interventions (73%; Table 5). Together, biological (18.44%) and drug-related (71.90%) interventions (including those that combine drugs with procedures, behavior, dietary supplements, or other interventions) account for roughly 90% of trial costs and 84% of all trials.

Table 4

Descriptions	Acute	Chronic
Length of Study	(62%) 1660 months	(38%) 1006 months
Costs	(57%) $282,429,811	(43%) $213,952,886
Patients with Condition	(89%) 52,546	(11%) 6,636
Number of Trials	(57%) 25/44	(43%) 19/44
Cost/Patients	$5,375	$32,241

Table 5

Descriptions	Summary Data
% trials Drug-related	(73%) 32/44
% trials Biological-related	(11%) 5/44
% Drug-related costs*	(72%) $356,901,558
% Biological-related costs**	(18%) $91,543,941

*Drug-related cost is defined as the sum cost of interventions including drug alone, Drug+Proc, Drug+Behav, Drug+Diet, Drug+Other, Drug+Proc+Behav, and Drug+Proc+Other
**Biological-related cost is defined as the sum cost of biological interventions such as stem cell and bone marrow cell therapy.

Among the 43 included trials, a total of 19,306 patients were enrolled. The mean number of patients per study is 449 and the average age of a study patient is 58 (Table 6). Average study duration is 58.53 months, or roughly five years, and average cost per cardiovascular clinical trial is $11.2 million. Adjusted for outliers, an average $25,000 is spent on each cardiovascular clinical trial patient.

Table 6:

Patient Descriptions Accounting for Outliers	Summary Data
Number of Studies	43
Total Number of Patients	19,306
Total Cost of All Studies	$483,338,477
Average Study Duration (Months)	58.53
Average Cost per Study	$11,240,430
Average # Patients/Study	449
Average Age	57.86
Cost/Patient (Excluding ^ patient Outlier)	$25,035
Range of Years	1999-2012

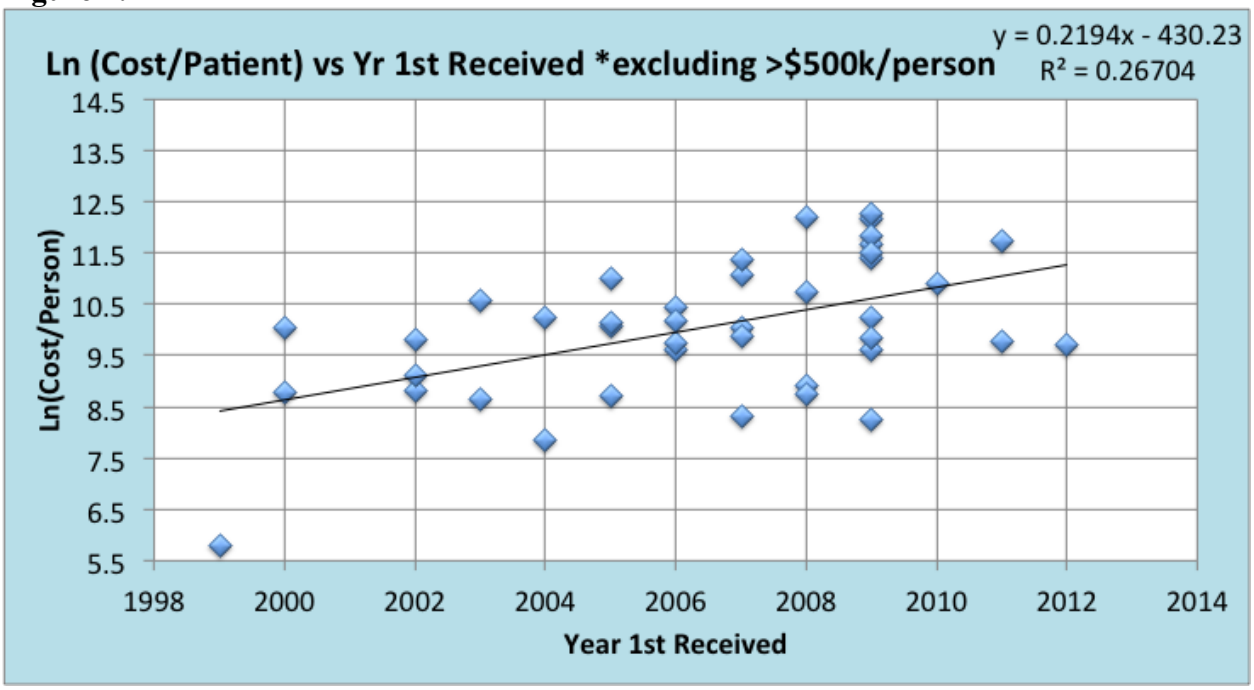
RESULT TRENDS:

Results suggest that over time, the cost of conducting cardiovascular clinical trials is increasing per patient. In the regression below, the ln(cost/patient) variable is computed by taking the natural log of each cost/patient variable per trial and running it against both number of participants and year first received. The coefficient in the natural log regression for "Yr first received" can be interpreted as a percent increase in cost/patient per year. When excluding trials that cost more than $500,000 per patient, a regression of ln(cost per patient) on the number of patients and year indicates a 14.56% yearly increase in cost per patient between 1999 and 2012 (Figure 1). Overall, costs per patient have been increasing with time.

Figure 1: Excluding $500k+ cost/patient trials

Ln (Cost/Patient)	*Coefficients*	*Standard Error*	*t Stat*	*P-value*	*Lower 95%*	*Upper 95%*	*Lower 95.0%*	*Upper 95.0%*
Intercept	-282.0646395	121.9228513	-2.3134682	0.02620366	-528.88455	-35.244731	-528.88455	-35.244731
Yr first received	0.14564731	0.060755538	2.39726804	0.02153972	0.02265415	0.26864047	0.02265415	0.26864047
Number of participants	-0.0000833	0.0000312	-2.6710253	0.0110704	-0.0001464	-0.0000202	-0.0001464	-0.0000202

Figure 2:



Between 1999 to 2012, the total costs of conducting a trial per year is downward trending, as is the length of study duration (Figure 3 & Figure 5). As expressed by the regression (Figure1) and shown by the graph in Figure 4, the numbers of patients enrolled in cardiovascular clinical trials per year is decreasing at a statistically significant rate of 0.00833% patients (or roughly 2 patients) per year. To explain the increasing costs per patients, one can look at the combined effect of decreasing total costs and a statistically significant decrease in patients. As the denominator decreases more significantly than the numerator, costs per patient rise. The following equation illustrates the impact of steep decreases in patient population on the costs per patient variable.

$$\uparrow Costs\ per\ patient = \frac{Total\ cost\ \downarrow}{Number\ of\ patients\ \ \downarrow\downarrow\downarrow}$$

Figure 3:

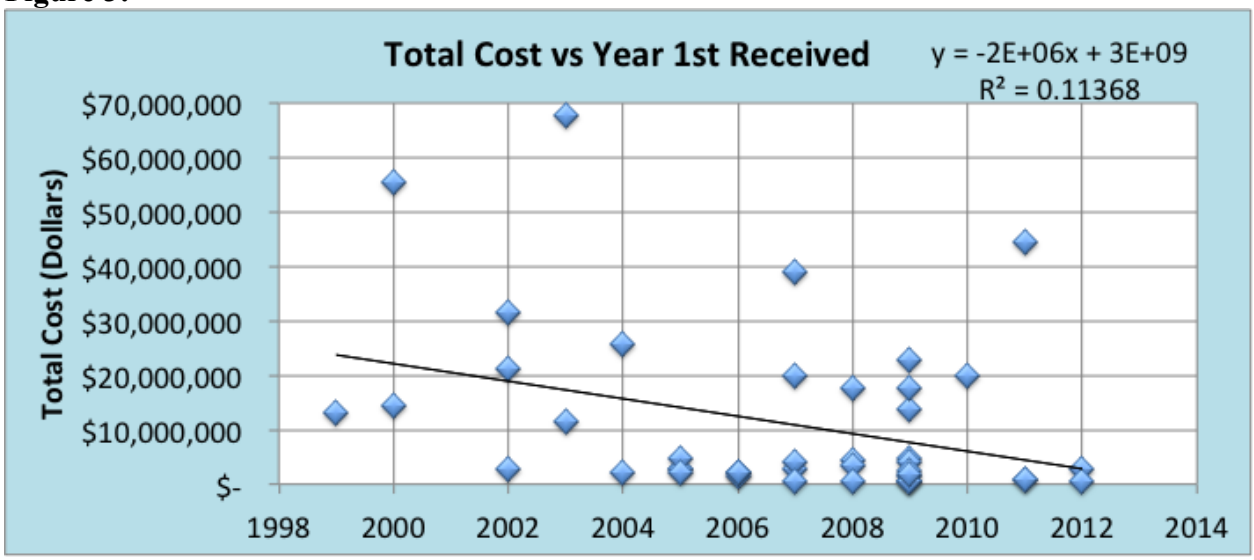


Figure 4:

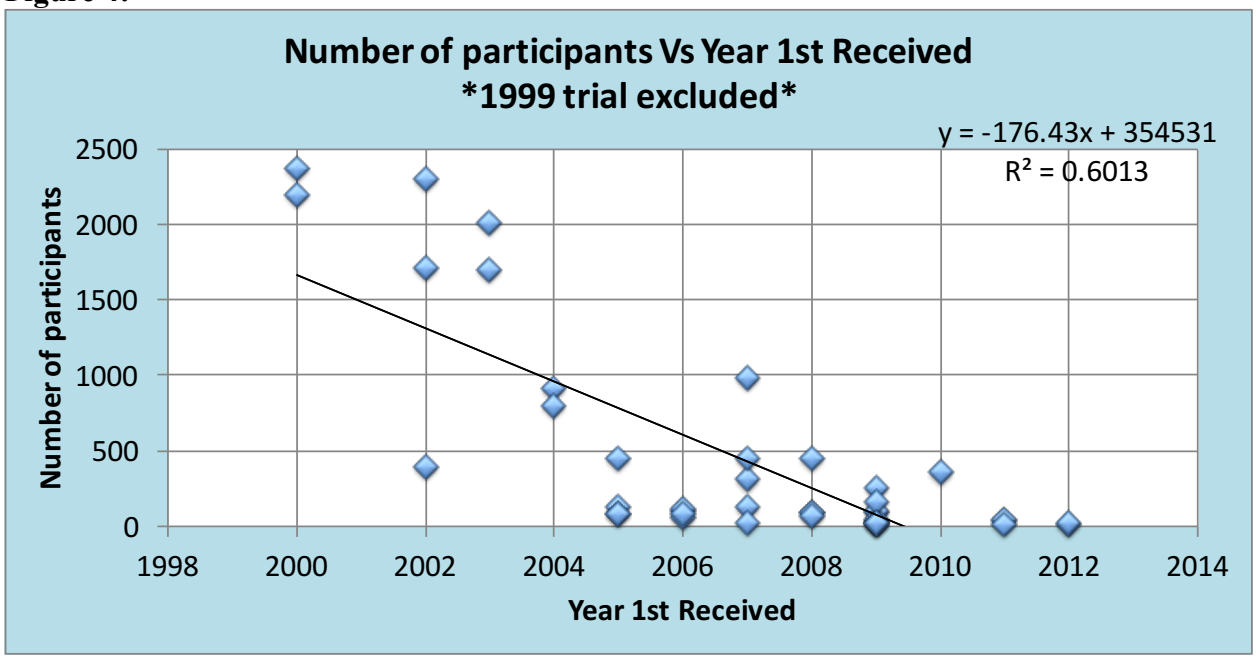
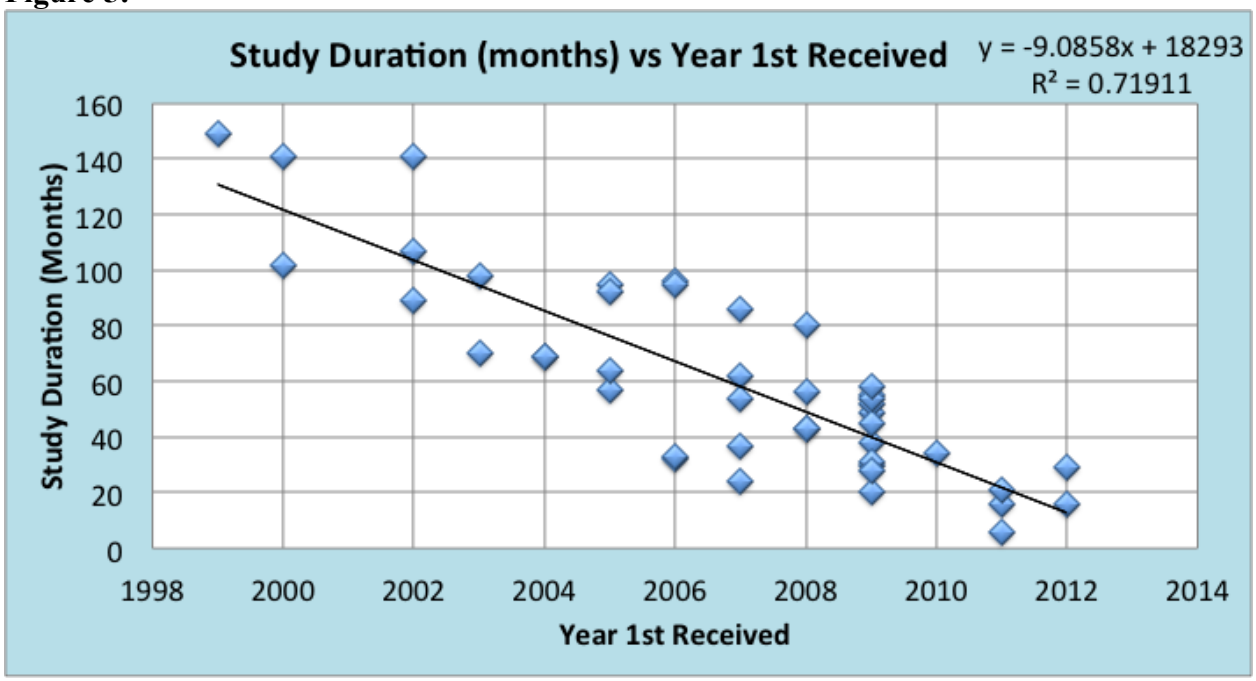


Figure 5:



DISCUSSION

Monitoring cardiovascular clinical trial spending is important as the United States seeks to maintain sustainable growth rates that increase population health, emphasize value in research, and address key CVD risk factors. This research serves to delineate trends in trials in order to promote further description of the field. It builds on previous literature and evolves from the key conclusion that clinical research is expensive (especially research involving or concerning technology and drugs). To recapitulate, results from this study indicate that total costs, patient enrollment, and study duration are decreasing while costs per patient are increasing.

One issue behind these trends may be limited funding. Limited funding leads to fewer patients enrolled in clinical trials (McDonald et al., 2006), as well as shorter clinical research trials due to constraints of personnel and time (Durivage & Bridges, 2009). Less time translates to fewer patients and higher costs per patient enrolled. Though current research has answered certain questions about the value of cardiovascular research in reducing heart-related disease, the cost characteristics of these trials merits further investigation.

The observed increase in costs per patient may have occurred for several reasons. Trials are becoming shorter in length and enrolling fewer patients, thus causing the trial costs to become more concentrated. This affects the unit costs of conducting research, promoting an increase in costs per patient. The initial hypothesis was that costs per patient would decline with an increasing use of, and familiarity with, technology. We predicted that costs per patient would decrease due to economies of scale, an overcoming of initial startup costs and spreading out costs over many patients. However, results contradict this initial hypothesis and data suggest that the initial hypothesis should be rejected. In accordance the concept of economies of scale, however, enrolling fewer patients leads to increased costs per patient.

The number of patients participating in CVD clinical trials is a critical factor in determining trial characteristics. Even though CVDs contribute to a small proportion of all trials (10%) compared to other diseases like cancer (contributing to roughly 50% of all trials conducted in the United States), CVD patient enrollment is greater, with an average of 275 patients per trial, compared to 20 per trial for cancer, 70 per trial for depression, and 100 per trial for diabetes (Griffin, Lebovitz, and English, 2010). As such, they are doing well in terms of patient recruitment compared to other clinical trials. Consequently though, changes in patient enrollment influence cost.

As a potential contributor to the aforementioned shift from government funding to industry funding, clinical trials are also subject to increased regulatory compliance and quality reporting from the FDA and NIH. Notably, this type of funding is critical in the initial stages of research as regulatory modifications here can have downstream effects on further scientific development. When it comes to drug development, increasing preapproval clinical safety testing to extend the duration of phase III clinical trials has been shown to negatively impact innovation and drug discovery (Reed et al., 2006). In addition, inconsistencies in NIH awards, often inadequate funding per trial site (sometimes 20-40% less than the actual cost of conducting trials), increased duration of research associated with navigating regulatory and administrative bottlenecking requirements, decreased clinical investigator workforce, and hardships in study patient retention all contribute to an inefficient clinical research process (Griffin et al., 2010). These challenges lead to wasteful practices and delays in clinical implementation, which translate to increased costs.

The results of this research serve to supplement the growing argument that cost per patient is increasing through the process of increased technology spending and increasingly complex

research regulations. This type of research is especially relevant for cardiovascular disease due to the high burden of disease and prevalence of high-tech interventional trials. In general, increasing trends in healthcare spending are extending into clinical trials and must be addressed accordingly. Potential solutions should ideally consider the full objective of gaining increased efficacy, practicality, and productivity without sacrificing trial safety. (Tunis et al., 2003).

Results from this study can also be used as indicators of solutions for policymakers and healthcare stakeholders looking to support the practice of evidence-based interventions. Previous research indicates that policymakers can address public health concerns by optimizing existing funding utilization, prioritizing new funding for trials that demonstrate impactful high-value parameters, and making informed health policy decisions based on practical clinical trials (Tunis et al., 2003). For example, collaboration of policymakers with nonpartisan scientific institutes to support appropriation of funding for trials can produce useful information that answers high priority questions and maximizes value (Tunis et al., 2003).

Clinical trial cost evaluation is also important to clinicians due to the translation of trial costs into treatment costs. Changes in medical organization and practice, such as the widespread adoption of managed care, have created increased pressure to reduce costs and created a demand for reviews and assessments (Tunis et al., 2003). In addition, practicing clinicians are urged to promote effective and predictable communication in order to maximize patient safety and quality care delivery (Leonard, Graham, & Bonacum, 2004). The goal of clinical research is, according to the NIH, to "enhance health, lengthen life, and reduce illness and disability" (National Institutes of Health, 2015). Considering these overlapping goals, increasing clinician interest in trials could provide a bridge to more economical and effective disease treatments. Though NIH funding in academic teaching centers is prevalent, increasing efforts to expand research to more

realistic clinical settings can be beneficial in maximizing value and benefits for clinical trial research (Tunid et al., 2003).

This pursuit for increased clinical research is now globalized and trials are increasing in geographic scope and complexity, gaining an increasing foothold and increased expenditure growth rates. In Asia-Oceania, composed of countries like China, South Korea, and Singapore expenditure growth rates 13% higher than those of the Unites States (Chakma et al., 2014). To maintain a competitive presence in the field of scientific research, the United States must continue to pioneer and coordinate efficient strategies that consider cost. Chakma et al. agree that increased coordination between the public and private sector is a viable means to maintain United States leadership in the field (2014).

Strengths and Limitations

A previous study by Berndt & Cockburn investigated the cost of conducting clinical trials using data from Medidata Solutions, Inc. and found that among biomedical research and development (R&D), grant cost per patient is increasing over time at a rate of 7.5% from 1989 to 2011 (2013). More importantly, they found that the growth rate of clinical trials pertaining to cardiovascular therapeutic areas in the United States increased at an average 14.1% between 2000 and 2011 (Berndt & Cockburn, 2013). Therefore, our results indicate an increase of 14.56% (described earlier as roughly 15%) per year from 1999-2012 are in agreement with previous literature. Study strengths include strict trial selection criteria, inclusion of impactful variables, and the analysis of transparent, traceable, and publicly available information.

Limitations of this partial evaluation study include concerns about sample size, indirect costs, and a few necessary assumptions. The small sample size provides a wide 95% confidence interval, and may have reduced generalizability as a limited, partial evaluation (Hackshaw, 2008; Kumar, Williams, & Sandy, 2006). Additionally, there were challenges to collecting data because even among government-only sponsors, individual trial funding data from United States Department of Defense (DOD) and U.S. Department of Veterans Affairs (VA) could not be traced, limiting the trial database to clinicaltrials.gov. According to previous literature, trial data from clinicaltrials.gov may sometimes show incomplete information, because up to 29% of registered trials remain unpublished (Roumiantseva et al., 2013; Jones et al., 2013).

More importantly, this study did not include indirect costs and costs associated with clinical phases that could have provided more information as to the factors impacting cost trends. Additionally, a major limitation is present due to the nature of analyzing study duration and participant enrollment by year first received. More specifically, those studies received more

recently by clinicaltrials.gov are faced with a temporal bias such that more recent trials are shorter and therefore have smaller durations and potentially less patient enrollment as well as costs.

Further studies investigating more complete figures on industry-inclusive funding, private donations, and outcome variables should proceed with acknowledgment of these limitations. Other research, such as a trial focusing on cancer trial costs per patient, looks beyond publicly available information and analyzes both disease progression and QOL in dually funded (government and industry) trials (Emanuel et al., 2003). Based on this study and others like it, future research may warrant investigating correlations between cardiovascular health outcomes, cost trends, and the effectiveness of different interventions on treatments, from a mixture of both public and industry sources.

FURTHER IMPLICATIONS

The trends of increasing costs per patient bring to light several concerning issues regarding public health interventions, and their failure to address CVDs in an efficient manner. With results of this study indicating that the costs of clinical trials for chronic CVD conditions are over $32,000 per patient, it is paramount that the further research address chronic heart disease for both economic and health reasons. From a health perspective, a major goal of research funding includes striving to prolong health and creating tangible benefits for patients. Major roadblocks in the dynamic between basic science research, clinical research, and improved patient health often prevent effectiveness and the smooth translation of new knowledge to treatment and clinical practice (Sung, 2003). Continuing clinical research is critical to patient health, especially patients with CVDs. For example, one study found that patients receiving treatment for acute coronary syndromes demonstrated higher compliance and lower mortality rates when treated in settings that actively conducted acute coronary syndrome clinical trials regardless of whether they were involved in the trials (Majumdar et al., 2008). Clinical trials also have import functions in assessing the role of costly technological and complex interventions (Krzyzanowska et al., 2011). Results from this study suggest that costs per patient are increasing. As costs per patient are increasing, it is possible that these cost trends could negatively impact patient treatment and medical care costs. Consequently, questions arise as to what factors that could influence cost changes, whether the current field of clinical research is sufficient at converting research dollars into health care savings and improving patient health as an end goal of clinical testing, and what can be done to address these concerns as they relate to patient care.

Pandya et al. argue that regardless of clinical research and decreases in disease mortality over time, prevalence, cost, and rates of disability related to CVDs in the Unites States are predicted to spike due to an increasingly aging population and rising rates of obesity and diabetes (2013). Specifically, these patterns could occur if the costs of obesity, diabetes, and age outweigh the benefits of recent smoking cessation trends and increased statin and antihypertensive treatment. (Pandya et al., 2013). Despite this, an unaccounted for, but potentially modifying propensity in this balance includes patient discipline and dedication to effective treatment protocols. Outside of the research setting, up to 25% of patients present with either partial or full non-adherence to antihypertensive drug treatment, thus compromising their blood pressure management and cardiovascular health (Tomaszewski et al., 2014). However, preventive measures like continuing antihypertensive and statin drug treatment, as well as halting rising obesity rates (maintaining BMI at a 2010 level), could prevent more than a million CVD cases from happening in the first place (Pandya et al., 2013). Proponents of preventive public health interventions such as smoking cessation and daily aspirin use, also advocate that maximizing preventive service utilization from current levels to 90% in 2006 could generate $3.7 billion in health savings (Maciosek et al., 2010).

It is clear then, that research costs, research effectiveness, and health outcomes are tightly interwoven with public health policy, such that the effects of increasing research costs per patient can be seen throughout societal strata. With the number of primary investigators (PIs) declining at 3.5% per year from 2001-2007, research capacity is decreasing (Getz, 2009). Additionally, patient enrollment is an increasing concern among the shrinking research investigator population. One study found that 52% of over 2,500 cancer trials at 14 sites could not enroll a single patient, (Durivage & Bridges, 2009). These challenges concerning persons involved in the research

process thus place a burden on medical care costs. However, it is important to continue clinical research because advancements can provide improved tools for evaluating drugs, devices, and medical ware (Woodcock & Woosley, 2008). Continued clinical research is justified due to the potential to identify superior interventions, improve healthcare outcomes, and estimate societal benefits (Krzyzanowska et al., 2011).

On the other hand, there must be careful consideration of subsequent increased costs that can impede the development of health improvements. The downstream effects of these implications often create inequalities when it comes to affording and accessing healthcare. For instance, medical expenses pushed 10 million Americans into poverty in 2010 (Short, 2011). In addition, the stress associated with a lower health, income, education, or occupational status can trigger the prolonged production of stress hormones that can lead to tissue damage and the onset of chronic diseases like CVDs and diabetes (Adler & Newman, 2002; Woolf & Braveman, 2011). Health inequalities and poor living conditions, especially early-childhood stress, can further socioeconomic challenges among many low-income Americans and increase the risk of developing CVDs like atherosclerosis later in life (Kaplan & Keil, 1993).

The solution to these issues may not be found in clinical or public health research alone, but rather in coordinated efforts relating practical cost data to effective interventions. As a secondary analysis of existing data, this study identifies a high cost per patient in conducting CVD research and argues the need for both research and societal cooperative support. To more effectively generate data on clinical trial outcomes and costs that can be used by scientists, public health officials, and policymakers, future trials should focus publishing research in a timely fashion, investigating clinical endpoints (Gordon et al., 2013), and simplifying trial design with large patient enrollments (Devereaux & Yusuf, 2013). Investigating the cost impacts of clinical

trials across international health care systems, wide patient demographics, and measuring specific outcomes may also lead to new insights into the factors impacting trial costs. Coupled with prevention and treatment policies, these types of trials can improve public health and address the risk factors for CVDs to alleviate the burden of disease. Though research converted into practice and coordination of prevention efforts across state boundaries to address hypertension, obesity, and diabetes, the CDC argues that targeting populations with CVDs could increase life expectancy in the United States by up to 7 years. (CDC, 2009) In the meantime, continued cost evaluation is needed to measure, characterize, and assess the inputs and outputs of clinical research in ways that generate a more informed perspective, as well as produce further insight on general population health and value in research.

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