

Comparative Effectiveness Research: Effect On Pharmaceutical Innovation, Value of Health and Longevity

John A. Vernon and Robert Goldberg

Section I: Introduction

Recent empirical research has quantified the impact that comparative effectiveness research (“CER”) could have, under various scenarios, on firm investment levels in pharmaceutical research and development (“R&D”) (Vernon, Golec, Stevens, 2010). In the current paper, we build directly from this published research and map the range of CER-induced reductions in R&D spending into their opportunity costs as measured by: (i) forgone life years; (ii) quality-of-life improvements; and (iii) dollars. In this paper, we will make two critical points: (1) the productivity of investment in pharmaceutical R&D is remarkably high—perhaps one of the most productive uses of capital in the economy; and (2) firm incentives to invest in pharmaceutical R&D will likely be very sensitive to the cost of conducting CER prior to and a condition of reimbursement and that as a result, incentives will be adversely affected. Taken together, these two points suggest the economic cost of new CER regulations will have a deleterious impact on social welfare, doing far greater harm than good. Our paper is organized as follows. Section II will present and discuss the evidence on the value of medical and pharmaceutical innovation. Section III will describe the research by Vernon *et al.* (2010) on the empirical link between pharmaceutical R&D investment levels and various CER regulation scenarios and simulations. In Section IV, we consider the evidence from the preceding two Sections, simultaneously, to obtain first-approximation estimates of the potential costs of future CER regulations in terms of life years and dollars. Section V concludes the paper and addresses an important consideration of our findings within the macroeconomic context of workforce (labor) productivity. In particular, we will discuss how pharmaceutical innovation (via R&D investment) is an important input to the economy’s production function. While this discussion will be at the highest, most generalized level, we will make an important observation: a more productive, healthy labor force could go a long way towards mitigating the impending (at least from a contemporary vantage point) collapse of U.S. social programs, such as Social Security and Medicare.

Section II: Value of Medical and Pharmaceutical Innovation

Recent research has uncovered some striking empirical findings on the economic value of medical and pharmaceutical innovation. For example, Yale University economist William Nordhaus (Nordhaus, 2005) has estimated the value of innovations in medicine during the second half of the twentieth century to be roughly equal to the gains in the economy’s real output, as measured by the Gross Domestic Product (“GDP”), over the same fifty-year period. The value of improvements in health (*e.g.*, life expectancy), unlike the economy’s real productive output of goods and services, is not reflected in national accounting statistics (which when aggregated will measure economic growth and national income, *i.e.*, GDP).

Nordhaus posits a simple, and indeed quite clever, question to demonstrate the intuitive reasonableness of his conclusion, which is based on highly technical research methods:

You must forgo either the health improvements over the last half-century or the non-health improvements. That is, you must choose either: (a) 1950 health conditions and 2000 non-health living standards; or (b) 2000 health conditions and 1950 non-health living standards. Which would you choose? (No need for quote marks when doing a block quote.)

Nordhaus, p. 389.

Choosing (b) or having a difficult time choosing between the two alternatives, Nordhaus observes, implies agreement with his research finding: the value of innovations in medicine in the U.S. from 1950 to 2000, approximately equaled the value of GDP gains (national income) from 1950 to 2000.

In another study, one that was prospective rather than retrospective, was conducted by the University of Chicago economists Kevin Murphy and Robert Topel (Murphy and Topel, 2006) who estimated the social-economic value of a 10 percent reduction in the mortality associated with cardiovascular disease and cancer around \$10 trillion (roughly \$4 trillion from reductions in cardiovascular mortality and \$6 trillion from reductions in cancer mortality). To place this number in perspective, note that the size of the U.S. economy, as measured by the GDP, surpassed the \$10 trillion level a few years ago, in the early 2000's. While this path-breaking research considered future reductions in mortality, it is not too speculative or too great of a leap to look backwards and recognize, for example, the effect that cholesterol-lowering statins have had on cardiovascular mortality in recent years.

To obtain an idea, if only to an order of magnitude, of the economic value statins have likely imparted to society, we consider the following illustrative example using the well-known Systematic Coronary Risk Evaluation ("SCORE") Equation (Conroy *et al.*, 2003).¹ The specified hazard model underlying SCORE is a Weibull distribution, estimated separately for subpopulations with and without coronary heart disease ("CHD"). Furthermore, age is modeled as exposure time to risk of death rather than as an independent risk factor. A general form of the model is depicted in equation (1):

$$P(M) = [S_0(\text{age})]^{\exp[X\beta]} - [S_0(\text{age} + 10)]^{\exp[X\beta]} \quad (1)$$

¹ There is vast literature on cardiovascular disease risk equations such as SCORE and Framingham, to name but two, and there is no shortage of critics of any of the equations. We selected the SCORE 10-year cardiovascular death risk equation for two principal reasons. First, even though the study was based upon a European population (Framingham was calibrated and estimated on data from a U.S. population), it focused on modeling mortality from cardiovascular disease as opposed to the development of cardiovascular disease, with a population. Secondly, it is based on more contemporary data which would, perhaps, result in more reliable model parameter estimates better reflecting recent years' population demographic profiles. We emphasize we are not weighing in on the contentious debates over the myriad risk equations and adaptations thereof, and are by no means endorsing the SCORE equation over other equations, such as the Framingham Risk Equation. Such judgments would be inappropriate as we are not experts in this area. This point cannot be overstated. Rather, we are only offering a simple retrospective analysis, based on one of the most ubiquitous risk equations, to demonstrate the order of magnitude of the likely economic benefits derived from the discovery, development, and launch of the statin drug class.

where P(M) is the 10-year probability of mortality from cardiovascular disease and X is a vector of independent risk factors, which includes cholesterol, systolic blood pressure, and current smoking status. Models were estimated separately for men and women, both with and without existing CHD (*i.e.*, high-risk and low-risk populations). Because our intent is only to be suggestive of the relative size to an order of magnitude of the economic value attributable to reduced mortality from cardiovascular disease—this is associated with the discovery and development of statins. To gauge, albeit in a non-scientific manner, the potential size of the economic benefits available to Americans when statins came to market, we present a range of average 10-year mortality risk reductions, for several subpopulation pre-statin risk profiles.²

To map the therapeutic benefits of statin therapy (principally low-density lipoprotein cholesterol, or LDL-C, reduction) into cardiovascular mortality reduction, we assume an average effect of a 40 percent reduction in LDL-C.³ Table 1 summarizes output from the SCORE hazard models for several subpopulations of non-smoking Americans.

Table 1: Statin-induced Percentage Reduction in Mortality from Cardiovascular Disease

Risk Factors/ Population	Total Cholesterol	Systolic BP	Age	10-Yr Mortality Pre-statins	10-Yr Mortality Post-statins	% Reduction in CVD Mortality
Men-CHD	200 mg/dL	140mm/Hg	50	2.46%	1.70%	30.9%
Women-CHD	200 mg/dL	140mm/Hg	50	0.63%	0.47%	25.4%
Men-No CHD	200 mg/dL	140mm/Hg	50	1.28%	0.91%	28.9%
Women-No CHD	200 mg/dL	140mm/Hg	50	0.40%	0.31%	22.5%

It needs to be emphasized that this analysis is intended only to be suggestive of the magnitude of economic benefits of statin technology. Using reasonable subpopulation cholesterol and systolic blood pressure average values for non-smokers, the ten-year reduction in mortality from cardiovascular disease ranges between 23 and 31 percent.

Murphy and Topel (2006) estimated that a 10 percent reduction in ten year mortality estimates would impart a \$4 trillion present value economic benefit). The hypothetical, retrospective reductions in mortality from statin technology in table 1 suggests it is not unreasonable to postulate that the 31 percent reduction in mortality over the past decade generates an economic

² There is a long list of factors that are not considered in this simple example and gross approximation. For example, we assume homogeneous sub-populations of Americans with identical cholesterol levels, systolic blood pressure, and age; all Americans begin statin therapy and maintain one-hundred percent compliance; and there is no countervailing Peltzman effect (that is, individuals are assumed not to modify their health behavior as a result of beginning statin therapy—for example, relaxing exercise and diet regimes because, on statin therapy, equilibrium CHD risk levels can be maintained with less exercise and poorer diets. Vernon and Golec (2011) discuss and analyze this phenomenon in detail.

³ 40 percent is approximately the average LDL-C reduction associated with the lowest available dose of atorvastatin 10mg (Lipitor™). Also, LDL-C reductions map into total cholesterol reduction via the well-known formula: TC = LDL-C + HDL-C + 0.20(Triglycerides).

benefit to Americans of a similar or greater magnitude. Similarly Vernon and Goldberg (2007) found that new drugs that would produce a 5-year delay in Alzheimer's disease (AD) onset for all new cases between 2010 and 2050 would be worth almost \$4 trillion (\$2006). Details regarding SCORE model parameter estimates, specifications, and functional forms may be found in the Appendix to this paper.

More direct, methodologically appropriate, and rigorous estimates of societal returns on investment in pharmaceutical research and development (R&D) have been studied by Lichtenberg (2004). In one widely-cited econometric study using data from 1960 to 2001, Lichtenberg estimated that every \$926 invested in pharmaceutical R&D “produced” on average, one additional life year in the population/economy. This is a very striking finding considering the fact that most government cost-benefit and cost-utility analyses assign a value of \$50,000 or higher to a year of life in good health. This startlingly high social rate of return to investment in pharmaceutical R&D implies more resources, private and or public, should be allocated towards this highly productive sector of the economy. In a later section of the paper, when we estimate the potential long-run economic costs that CER regulations may inadvertently impose on society, via reduced research incentives, we will rely upon Lichtenberg’s measure of pharmaceutical R&D productivity to map forgone R&D into forgone life years and dollars.

Our research is more relevant now because the underlying assumption of CER is that many new drugs, devices, and other technologies greatly increase the rising healthcare costs even as they contribute little clinical benefit relative to a previous generation of products. Many observers maintain that the increase in healthcare spending is the result of the development and overuse of new medicines, devices, and diagnostics. In making this case, proponents of this view make three assumptions. First, that most of the ‘overuse’ does not improve health or extend life. Second, that CER information about the costs, risks, and benefits of different treatment options, combined with new incentives reflecting the information, could eventually alter the way in which medicine is practiced and yield lower healthcare spending without having adverse effects on health. Over the long-term, the potential reduction in spending below projected levels could be substantial. Third, CER can be used so “that Medicare spending—and perhaps all health spending in the country—could be cut by about 30 percent if the more conservative practice styles used in the lowest-spending one-fifth of the country could be adopted nationwide.” CBO (2007)

Based on these assumptions, the Patient Protection and Affordable Care Act both requires the development of CER and its use in defining healthcare quality and in making coverage decisions. Some of the strongest proponents and contributors to the body of CER “as Congress moves toward substantial reductions in Medicare spending, the program will be under increasing pressure to ensure that dollars are directed to services providing known benefits.”

Lichtenberg (2009) notes:

Some observers argue that rapidly increasing healthcare expenditure is due, to an important extent, to medical innovation – the development and use of new drugs, diagnostics, and procedures. For example, the Kaiser Family Foundation (2007), citing Rettig (1994), claims that “advances in medical technology have contributed to rising overall US healthcare spending.”

Other observers argue that most medical innovations do not improve peoples' health. Lexchin (2004), for example, claims that "at best, one-third of new drugs offer some additional clinical benefit and perhaps as few as 3% are major therapeutic advances." If both of these claims were true, medical innovation would result in the worst of both worlds – a large increase in cost and little or no increase in benefit (in the form of improved health outcomes)."

Yet, the evidence presented in this section of the extraordinary economic value attributable to medical and pharmaceutical innovation, both past and future (potentially) establishes that "that medical innovation has yielded significant increases in life expectancy." Further, the social value of living longer and healthier lives actually increases at a faster rate as a result of consuming increasingly more effective products that delay or prevent disease for relatively less money. As Fogel (1997, 2007) and others have documented, increases in the efficiency and diffusion of medical innovations over the past century have allowed humans to work less while producing more and therefore living longer while enjoying a growing number of leisure activities more often with less money.

We believe that public policy affecting drug development investment incentives consistently fails to capture the value of this well-documented – and increasing – contribution of medical innovation to human progress. Part of the problem is that the physiological changes in human "sustainability" produced by medical innovations are hard to observe. Fogel notes: "Although these changes have been rapid from an evolutionary perspective, little of the pattern of change is visible over a couple of decades." It must be well-informed, balanced, and transparent. While special interest groups and political agendas are here to stay (which is not a bad thing *per se*, as we know from public choice theory), making inroads on the public misinformation surrounding pharmaceutical innovation and its value to society, which result in distorted characterizations of the economics of drug development. Moreover, the increases in the social value of health and longevity sustain a growing demand for healthcare services. Ironically and not unexpectedly, healthcare costs are the focus of most policy considerations because this demand is heavily subsidized by taxpayers. This subsidy, rather than the value of what is spent on healthcare is the main concern of legislators.

We propose to address the interaction between the social value of medical innovation and retirement policy in a future paper. More immediately, requirements to conduct and use CER to control rising costs and expand the number of people receiving subsidized health by slowing the development and diffusion of medical innovation could actually increase healthcare spending and have a deleterious effect on human progress. Our paper focuses on CER not only because proponents maintain it can be used to improve health outcomes and reduce cost, but in addition, the underlying assumption of CER is at direct odds with empirical evidence that medical innovation – not regulation – increases life expectancy and reduces the cost of services needed to obtain such gains.

Section III: Modeling Possible CER Regulations and R&D Investment

Vernon, *et al.*, (2010) have demonstrated how CER regulations have the potential to result in increasing clinical trial sizes (and costs) and perhaps clinical development times; the latter would increase the cost and risk of drug development from an investment decision making perspective. As the authors caution, their analysis is simple, but it does demonstrate, in a very basic way, the

simple mathematics of clinical trial sample size requirements; requirements that may result in several fold increases in clinical trial sizes. CER can increase the complexity of clinical trials, the number of people enrolled in a clinical trial, and the number of studies conducted after a product receives approval. In Europe, “approximately one-fourth to one-third of the regulatory costs are estimated to go toward the reimbursement issue.

Further, CER can delay time to market and reduce the rate and extent of technology diffusion. A recent study (Mason, 2010) looked at the impact of CER on market access and found the process delayed use by over two years. Moreover, the same study found that CER use as part of reimbursement decisions in cancer was associated with 60 percent fewer medications being made available than when such reviews were not used.

CER also adds to the risk of investing because it increases the uncertainty about whether a product will enter the market. The uncertainty ranges “from the impossibility of demonstrating the full scope of a product’s value at the time of authorization, through to the impossibility of knowing precisely what will be on the market (and how good it is compared to your product) by the time you reach the point of seeking authorization. As research departments and company finance officers have frequently lamented, there is a profound discouragement to innovation when every new product runs the risk of flat rejection by regulators at the last minute, because of some unforeseeable arrival of another, arguably superior, therapy just before you seek authorization (O’Donnell, 2010).

From a firm R&D investment decision making process, this will make more developmental R&D projects less attractive; that is, with higher expected drug or device development costs, slower access to market and increased uncertainty, fewer R&D projects will have positive Net Present Values (NPVs). As a result, equilibrium R&D investment levels will decline, and the rate of pharmaceutical innovation will slow. We illustrate this more formally below.

For any given potential R&D project, firm managers assess the expected NPV of a project. In Equation (2) below, $c(t)$ denotes the cash flow at time t , $p(c; t)$ is the probability density function associated with cash flows, and r represents the firm’s opportunity cost of investment capital.

$$E(NPV_0) = \int_0^T p(c; t) c(t) e^{-rt} dt \quad (2)$$

Pre-launch cash flows are negative, with the largest negative cash flows occurring during Phase III of clinical trials, and which are the largest trials because they are used to demonstrate safety and efficacy versus placebo to the Food and Drug Administration (“FDA”). Post-launch cash flows are positive as they capture net sales revenues from the new product after launch. If a project has a positive expected NPV, firms will select to undertake the R&D project, or at a minimum, continue the project until another NPV analysis is undertaken with updated information. The effect on firms, directly or indirectly, of having to bear some or all of the costs of CER trials will be that fewer R&D projects will have positive expected NPVs. Figure 1 below illustrates the equilibrium R&D investment level selected by firms (this figure is an adaptation from Vernon and Golec (2009), AEI Press, Washington, D.C.).

Figure 1: Potential Impact of Comparative Effectiveness Regulations on Equilibrium R&D Investment

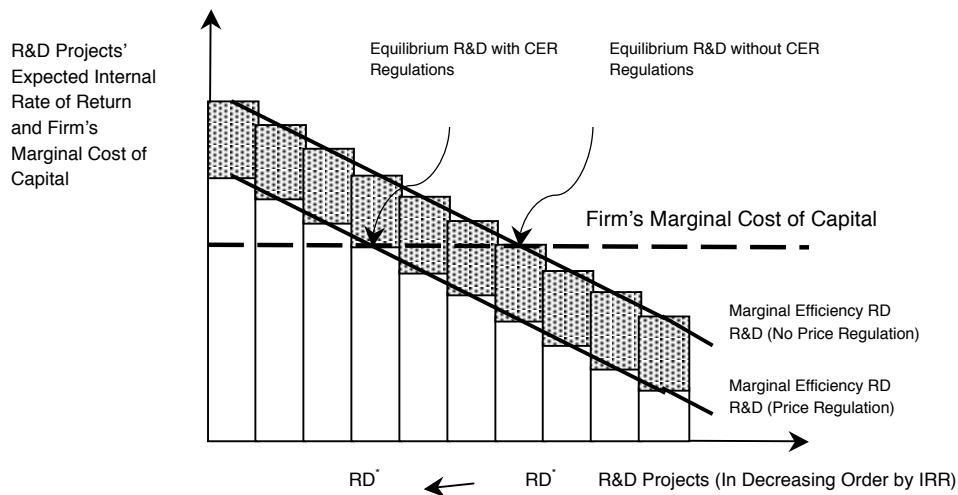


Figure 1 demonstrates that fewer R&D projects make financial sense to undertake if clinical development costs and risks rise substantially because of CER regulations. As clinical development costs rise, fewer and fewer R&D projects will be profitable from an NPV perspective. Firms will undertake the high return projects first and continue to undertake additional investment projects so long as the expected rate of return from the next project (its internal rate of return (“IRR”)) exceeds the firm’s marginal cost of capital, meaning that fewer of the projects further to the right in Figure 3 [should this be Figure 1?] will “pay off.” Higher expected clinical development costs, as a result of CER regulations, will shift the marginal efficiency of R&D curve (demand curve for R&D) to the downward and a lower equilibrium level of R&D will result.

To approximate the impact that CER regulations may have on the cost of drug development, and hence firm incentives to invest in R&D, we consider how such regulations could affect pharmaceutical profit margins, which have been identified as the key determinant of pharmaceutical R&D expenditures. We next summarize, using an earlier version of our recently published analysis (cited above), how CER regulations may inadvertently reduce firm-level investment in pharmaceutical R&D, *ceteris paribus*.

Measuring the effect CER regulations may have on pharmaceutical profit margins allows us to trace their potential impact on R&D expenditures via recent empirical models of the determinants of pharmaceutical R&D investment intensity. However, it should be emphasized first that we employ several assumptions that necessarily are speculative; but our objective is not to obtain precise estimates – rather, we seek only to obtain a first approximation of magnitudes of effect that might be involved.

To begin, we note that a new drug costs approximately \$1 billion (US) to bring to market. Of course, both higher and lower estimates exist (DiMasi, Hansen, and Grabowski, 2003; Vernon, Golec, and DiMasi, 2010). According to the 2009 PhRMA Industry Profile, approximately

28.5% of industry R&D expenditures come from Phase III clinical trials – the most likely development stage where CER trials would be undertaken. Based on our previously published clinical power analyses (Vernon, Golec, Stevens, 2010), we can estimate how CER regulations may impact Phase III trials and increase total R&D expenditures, on average. Using the aforementioned 28.5% component of annual R&D expenditures that are associated with Phase III trials, we consider a range of increased Phase III trial costs and how they affect total drug development costs. Using this in conjunction with data on average industry profit margins and average industry R&D intensity (pharmaceutical R&D expenditures divided by pharmaceutical sales) we will derive the proportion of total pharmaceutical business segment costs that are R&D costs. We then can map the increased Phase III clinical trial costs into its affect on pharmaceutical profit margins. Having done this, it is straightforward to then approximate how pharmaceutical R&D expenditures (intensities) are affected using the empirically established relationship between R&D intensity and industry-level pharmaceutical profit margins from Grabowski and Vernon (2000). Other studies have used similar models, but this is the only one that used industry-wide pharmaceutical business segment profit margins and development costs – the measure we use here.

According to a 2009 industry audit, the industry’s average pharmaceutical gross profit margin (gross pharmaceutical sales less costs, all divided by gross pharmaceutical sales) was 31.4%. For the same year, average pharmaceutical R&D intensity was reported to be 17.5%. To trace the effect of higher Phase III clinical trial costs, which increase average drug development costs and thus, total pharmaceutical business segment costs, into gross pharmaceutical profit margins, consider the following: where gross margins are decomposed into price cost margins below, where p is defined to be gross pharmaceutical profits, s is defined as pharmaceutical sales, and p and q are the familiar variables price and quantity, respectively.

$$\frac{\pi}{s} = \frac{p \times q - c \times q}{p \times q} = \frac{q(p - c)}{p \times q} = \frac{p - c}{p} \quad (3)$$

Defining the gross margin (0.314) in equation 3 as θ , and defining pharmaceutical R&D intensity (ratio of R&D-to-sales) as λ , it is straightforward to obtain a measure of ratio of pharmaceutical R&D costs to total pharmaceutical business segment costs (inclusive of R&D expenditures). We define this cost ratio as ρ . It is necessary to derive ρ in order to map the factor increase in R&D costs into pharmaceutical price cost margins. It is straightforward to show, with simple algebraic manipulation and substitution,

$$\rho = \frac{\lambda}{1 - \theta} = \frac{0.175}{1 - 0.314} = 0.255 \quad (4)$$

which is the fraction of total pharmaceutical business segment costs that are impacted by higher clinical development costs (through higher Phase III clinical trial costs in the context modeled here). Before we present our first approximation results in table 2, we note that the co-efficient estimate on the Grabowski and Vernon (2000) gross pharmaceutical margin variable was 0.73 (t-statistic =10.59). Based on their levels specification, this implies that for every percentage point reduction (increase) in gross pharmaceutical margins, R&D intensity declines (increases) by 0.73 percentage points, or 0.0073. Our estimates of the impact of CER on profit margins and R&D

intensity are summarized in table 2, based on indexed Phase III clinical trial costs from 1.5 to 3.5 from Vernon, *et al.* (2010).

Table 2: Comparative Effectiveness Regulations,
Pharmaceutical Price cost Margins, and R&D Investment

Phase III trial Costs	Total R&D Costs	Impact on profit Margins*	Impact on R&D Intensity
1.0	1.00	0.000	0.000
1.5	1.14	-0.024	-0.017
2.0	1.29	-0.049	-0.036
2.5	1.43	-0.074	-0.054

* The impact on price cost margins or pre-tax gross pharmaceutical margins, is estimated by treating total pharmaceutical costs as the numeraire (which is decomposed into an R&D cost component and all other pharmaceutical business segment costs). Higher drug development costs will impact total pharmaceutical operating costs and allocated fixed pharmaceutical business costs in the denominator of the price cost margin (which includes R&D costs), and therefore, also the price cost differential in the numerator. In the short run, the price variable is assumed to be unaffected by increased R&D costs because, at the time a pharmaceutical product reaches the market, R&D costs are sunk. It is also assumed that the non-R&D cost component also remains unchanged. This enables us to obtain a measure of the impact that higher Phase III clinical trial costs have on price cost margins. This highlights one of the limitations of price cost margins as a measure of expected future returns (profitability) to R&D, as discussed in Vernon (2005) and Vernon, *et al.* (2009). This point noted, and as a means of a first approximation of the impact that comparative effectiveness regulations may have on equilibrium R&D intensity, we rely on the mechanical link, as estimated by Grabowski and Vernon (2000) to map lower price cost margins into R&D intensity. Finally, note that higher Phase III R&D costs in isolation (ignoring equilibrium levels), raises the numerator in the ratio of pharmaceutical R&D to pharmaceutical sales, but clearly our approximation is a measure of the total effect on R&D intensity, which reflects both higher average R&D costs per new drug, and the dominating effect of lower numbers of R&D projects undertaken and/or advanced through development, due to their failure to satisfy the positive expected NPV criterion.

The results in table 2 demonstrate quantitatively how, through a series of basic cause and effect relationships, R&D investment can be affected by higher drug development costs due to larger Phase III clinical trials designed to detect a statistically significant efficacy differential between a developmental product and a comparator, as opposed to placebo (see Vernon, Golec, and Stevens, 2010). If CER regulations result in a 50 percent increase in Phase III clinical trial costs, total R&D costs would increase by approximately 15 percent, profit margins would decline by roughly 2.5 percentage points, and the impact on R&D intensity would be a decline of about

0.017, or 10% (based on an initial R&D intensity of 0.175). These estimates are intended to only be illustrative and to highlight a possible consequence of future CER regulations and/or policies. It is not at all clear that such future regulations or policies would result in firms bearing the cost of more head-to-head clinical trials, but it should be noted that funding for such head-to-head studies, including those organized by the National Institute of Health, is provided largely by private companies. Moreover, the cost of developing the evidence of new drug or a device's clinical benefit for the Medicare program is borne by the company. Increasingly, companies are changing the design of studies knowing the FDA and the Center for Medicare and Medicaid Services (CMS) will be sharing data for purposes of product approval and reimbursement. Most importantly, though rarely noted, CER will be used by health exchanges and the government in determining what health services and products will be covered under the new health care law. Hence, shedding light on the possible consequences of such a potential eventuality is important. This is especially true when one considers the evidence on the value of pharmaceutical innovation, medical innovation more generally, and that the added cost and uncertainty will increasingly be assumed by small firms operating at a loss.

Section IV: Potential Costs of CER Regulations from Forgone Innovation

In the previous two sections, we have documented two principal facts: (1) the economic productivity, in terms of the social benefits bestowed, of medical and pharmaceutical research is extraordinarily high. As noted, Lichtenberg (2003) finds that *the periods during which the most new drugs have been approved by the FDA tend to be the periods in which longevity grew most rapidly*. This suggests that the greater the number of drugs that are available to physicians and consumers, the higher longevity will be. As noted earlier, Lichtenberg finds that for every \$926 investment in pharmaceutical R&D produces one U.S. life year and that pharmaceutical embodied technical progress has a tendency to reduce inequality as well as promote economic growth;* (2) CER regulations have the potential to significantly reduce levels of pharmaceutical R&D investment. Taken together, these two facts can lead to only one conclusion: CER regulations pose a clear and present threat to social welfare. A simple analysis will demonstrate that this threat is, potentially, a very costly one indeed. We consider the case in which new CER regulations, either directly or indirectly, result in Phase III clinical trial costs increasing by fifty percent. This scenario is summarized in table 2 and was described in the previous section. Tracing the causal relationships from higher Phase III clinical trials costs, to higher (expected) total R&D costs, to lower (expected) pharmaceutical profits, to lower equilibrium levels of firm R&D intensity, the result is a 10 percent decline in R&D intensity.

We consider analyzing the impact of R&D growth rate declines resulting from CER regulations, with two distinct models. These models can be used to compute the present value of R&D

* Lichtenberg writes: The estimates indicate that the average new drug approval increases the life expectancy of people born in the year that the drug is approved by .016 years (5.8 days). This may sound insignificant, but since there are approximately 4 million births per year in the United States, the average new drug approval increases the total expected life years of the cohort by 63.7 thousand years (4 million births times .016 years/birth). New drug approvals in a given year also increase the life expectancy of people born in future years, but by a smaller amount (because of obsolescence of drug s). I estimate that *current and future generations will live a total of 1.2 million life years longer because of the average new drug approval*.

expenditures under different R&D growth assumptions and declines. The models provide estimates of cumulative effects on R&D spending over multiple-year periods. The first model reflects an R&D growth rate drop from its current fixed long-term rate, to a new lower long-term rate.

The model is:

$$PVRD_t = \frac{RD_{t+1}}{(r - g)} \quad (5)$$

where RD_{t+1} is next year's pharmaceutical R&D spending, $PVRD_t$ is the present value of future pharmaceutical R&D spending, r is the discount rate associated with R&D spending flows, and g is the constant future growth of R&D spending.

The second model is used to evaluate and compare R&D spending over short periods of time.

The model is:

$$PVRD_t = \frac{RD_{t+1} \left[1 - \frac{(1 + g_s)^n}{(1 + r)^n} \right]}{(r - g_s)} \quad (6)$$

where g_s is the short-term growth in R&D spending from year t through year n .

According to the industry trade group, PhRMA, total pharmaceutical R&D spending by its member firms in 2009 was approximately \$45 billion. Scherer (2001) has measured the average annual real growth rate of pharmaceutical industry R&D spending to be approximately seven percent. Recent research on the real cost of capital for the pharmaceutical industry suggests a plausible measure of roughly 13 percent (Vernon, Golec, and DiMasi, 2010; Giaccotto, Golec, and Vernon, 2011). Using these measures, we calculate present value forgone R&D associated with a one-time decline in pharmaceutical R&D of 10 percent (modeling divergent growth rates instead of a one-time decline is also possible, but for the sake of simplicity and transparency, we model a one-time adjustment in the equilibrium level of R&D investment). For the short-term model, we consider a 10-year time horizon. Table 3 reports our calculated present value forgone pharmaceutical R&D estimates.

Table 3: Present Value Forgone Pharmaceutical R&D Resulting from CER Regulations

Model	PVRD No CER Regs	PVRD with CER Regs	PVRD "Lost"
Short-term Model (10 Years)	\$315.4 Billion	\$283.8 Billion	\$31.6 Billion
Long-term Model (Perpetuity)	\$750 Billion	\$675 Billion	\$75 Billion

Based on the assumptions presented thus far, we generate first-approximation estimates of the present value of forgone pharmaceutical R&D that would be associated with (caused by) new CER regulations that drive Phase III clinical trials cost up by 50 percent. Over a 10-year time horizon, the forgone R&D would be \$31.6 billion; in perpetuity, present value forgone R&D would be \$75 billion. These estimates are indeed speculative, but the assumptions are conservative, and it is the order of magnitude of the long-run costs of forgone pharmaceutical R&D to which we wish to draw attention.

The estimates in table 2 of forgone present value pharmaceutical R&D investment can be linked directly to the aforementioned study by Lichtenberg (2004), whose productivity measure of pharmaceutical R&D investment finds that for every \$1345 invested in R&D produces an additional life year in the U.S. While Lichtenberg's estimate is an average productivity measure and not a marginal one, it is an average productivity measure associated with a production function that is constantly shifting outward, and not based upon incremental R&D spending at a point (or year) in time—where diminishing returns characterize innovative returns to marginal R&D investment. That is, consistent with empirical research conducted by Fogel, Murphy and Topel and others, Lichtenberg shows that pharmaceutical innovation continually increases life expectancy. This is a critical point that cannot be emphasized enough. For this reason, it is reasonable to build off his work within the context of forgone present value R&D shown in table 2. We do this and report our results below in table 3.

Specifically, we map forgone R&D into forgone life years and dollars. To translate life years into dollars we use the conservative assumption that a life year is equal to \$50,000. While much higher estimates exist, we are opting to be conservative in all of our assumptions so that our estimates may plausibly be viewed as lower-bound approximations.

Table 4: Present Value Costs of CER Regulations in U.S. Life Years and Dollars

Model	PV “Lost” R&D	“Lost” Life Years	PV Cost to Economy
Short-term Model (10 Years)	\$31.6 Billion	34.06 Million	\$1.70 Trillion
Long-term Model (Perpetuity)	\$75.0 Billion	80.99 Million	\$4.05 Trillion

Given the remarkable productivity associated with pharmaceutical R&D, it is not surprising that our estimates place the present value cost to society of a 10 percent reduction in R&D, resulting from new CER regulations, between \$1.7 trillion and \$4 trillion. Any new or proposed policy with the potential to impose such high costs on society needs to be evaluated closely, especially given the focus on using CER to “bend the cost curve” downward. As Nordhaus (2005) has demonstrated, the trajectory of innovation in medicine and healthcare over the past 50 years have imparted benefits to the U.S. that have been roughly equivalent to the economic value of all non-health improvements in our standard of living and national income, which, unlike gains in life expectancy and improvements in quality of life, are carefully measured by national accounting data and statistics, and comprise the nation’s annual Gross Domestic Product (GDP).

Section V: Conclusions

In this paper, we have provided evidence to support two important conclusions. First, the economic value associated with medical and pharmaceutical investment and innovation are staggering. We discussed research by Lichtenberg (2004), Murphy and Topel (2004), Nordhaus (2005), (Fogel, 2006) as well as others, who have estimated the economic productivity of medical and pharmaceutical investments and innovations. Their findings are astonishing and leave little doubt advances in medicine and pharmaceutical technology have bestowed enormous socio-economic benefits to patients, economies, and society. Second, a theoretical and empirical link exists between potential CER regulations and the industry-level of equilibrium investment in pharmaceutical R&D.

Agreement with both of these conclusions implies agreement with their unambiguous corollary: CER regulations pose a clear and present threat to social welfare. If CER regulations and policies are advanced and implemented with a blind eye towards their effect on long-run innovation, the socio-economic cost to society could be detrimental. We approximate the magnitude of this cost to be in the trillions of dollars.

Also, an important and largely overlooked role of pharmaceutical investment and innovation is as a critical input into the production function of the U.S. economy. Specifically, pharmaceutical innovation is an important determinant of labor force health and productivity. We demonstrate this in equation (7) where economic output (Y) is a function of current technology, T, real (physical) capital, K, and labor, $L[I(RD), X]$, which is a function of pharmaceutical innovation (itself a function of R&D investment), and other variables (vector X).

$$Y = T[L [I_p (RD), \mathbf{X}], K] \quad (7)$$

The opportunity costs of forgone innovation can be cast within the context of the production function shown in equation (7). Medical and pharmaceutical innovations have directly improved the productivity of the U.S. workforce and labor supply (in the current discussion we consider only frictional and voluntary unemployment). A healthier workforce has lower levels of absenteeism and “presenteeism” (e.g., see the research by Berndt, *et al.* with respect to depression), it is more productive, and as life expectancies increase, the length of the average productive, healthy work life also expands.

A healthier U.S. workforce, as a result of pharmaceutical innovation, may also mitigate to some degree the impending financial crises threatening the future solvency of precarious government social programs, such as Social Security and Medicare. Research by Lubitz, Cutler and others show, for example, that Medicare beneficiaries at age 70 with no reported disabilities, live three years longer but consume fewer medical services than beneficiaries at the same age but have at least one disability. Any government policies or regulations that impede the progress of medical innovation, such as potential CER regulations, are likely to exacerbate the challenges of supporting and ensuring the survival of such social programs. In this regard, of course, effects would occur in the long-run. Indeed, from a political perspective, perhaps this underlies the greatest challenge to balanced and socially-optimal public policy. The uncertainty associated with technological progress and medical progress, in particular, along with the long-time horizons associated with pharmaceutical innovation, result in considerable vulnerability to sound public policy; public policy that fosters market-based incentives for biopharmaceutical innovation in what is, perhaps, one of the highest return-on-investment sectors of the U.S. economy. Myopically-focused political agendas and the failure to recognize the underlying economic value of innovation are forces that need to be overcome, or at least tempered, if society is to allocate resources in an efficient, social welfare optimizing manner. In sum, while at this time it remains unclear if and how CER will be implemented in the U.S., it is critical to recognize and acknowledge that threats to innovation do exist and are balanced fairly in the policy debate.

REFERENCES

- [1] Lichtenberg, F. (2004) "Sources of U.S. Longevity Increase, 1960-2001" *Quarterly Review of Economics and Finance* 44(3): 47-73
- [2] Murphy, K. and Topel, R. (2006) "The Value of Health and Longevity" *Journal of Political Economy* 114(5): 871-904.
- [3] Nordhaus, W. (2005) "Irving Fisher and the Contribution of Improved Longevity to Living Standards" *The American Journal of Economics and Sociology* 64(1): 367-92.
- [4] Vernon JA, Goldberg R, Golec J. Economic evaluation and cost-effectiveness thresholds: signals to firms and implications for R&D investment and innovation. *Pharmacoeconomics* 2009; 27 (10): 797-806
- Mason A, Drummond M, Ramsey S, Campbell J and Raisch, D Comparison of Anticancer Drug Coverage Decisions in the United States and United Kingdom: Does the Evidence Support the Rhetoric? *Journal of Clinical Oncology*, July 10, 2010 vol. 28 no. 20 3234-3238
- [5] Murphy KM, Topel RH. The economic value of medical research. In: Murphy KM, Topel RH, editors. *Measuring the gains from medical research: an economic approach*. Chicago (IL): University of Chicago Press, 2003: 41-73
- [6] Vernon, JA, Goldberg R, Dash, Y, Muralimohan G. Alzheimer's Disease and Cost-effectiveness Analyses: Ensuring Good Value for Money? http://www.act-ad.org/pdf/Study_Final_051407.pdf
- [7] Grabowski HG, Vernon JA. The determinants of pharmaceutical research and development expenditures. *J Evol Econ* 2000; 10: 201-15
- [8] Vernon JA. Examining the link between price regulation and pharmaceutical R&D investment. *Health Econ* 2005; 14: 1-16
- [9] Giaccotto C, Santerre R, Vernon JA. Drug prices and R&D investment behavior in the pharmaceutical industry. *J Law Econ* 2005; 48: 195-214
- [10] Vernon JA, Golec JH. *Pharmaceutical price regulation: public perceptions, economic realities, and empirical evidence*. Washington, DC: AEI Press, 2009
- [11] Vernon JA, Golec JH, Lutter R, et al. An exploratory study of FDA new drug approval times, prescription drug user fees, and R&D spending. *Q Rev Econ Fin* 2009; 49: 1260-75
- [10] Golec JH, Hegde S, Vernon JA. Pharmaceutical R&D spending and price constraint threats. *J Fin Quant Analysis* 2010 Feb; 45: 239-64
- [12] DiMasi JA, Hansen RW, Grabowski HG. The price of innovation: new estimates of drug development costs. *J Health Econ* 2003; 22 (2): 151-85

[13] Vernon JA, Golec JH, DiMasi J. Drug development costs when financial risk is measured using the Fama-French three-factor model. Health Econ. Epub 2009 Aug 4

[14] Pharmaceutical Research and Manufacturers of America. Pharmaceutical industry profile 2009. Washington, DC: PhRMA, 2009 Mar

[15] Lichtenberg FR. Sources of US longevity increase, 1960–1997 [NBER working paper no. 8755]. Cambridge (MA): National Bureau of Economic Research, 2002 [online]. Available from URL: <http://www.nber.org/papers/w8755> Accessed 2010 May 17]

[16] Lichtenberg FR. The impact of new drug launches on longevity: evidence from longitudinal disease-level data from 52 countries, 1982–2001. Intl J Health Care Fin Econ 2005; 5: 47-73

[17] Vernon JA. New estimates of the cost of drug price controls. Regulation 2004; 14: 1-16

[18] Pharmaceutical Industry Audit 2009. Pharma Exe. 2009 Sep [online]. Available from URL: <http://www.scribd.com/doc/23086153/Pharmaceutical-Industry-Audit-2009> [Accessed 2010 May]

[19] Pharmaceutical Research and Manufacturers of America, 2010, “Pharmaceutical Industry Profile: 2010”. Washington D.C.

[20] Congressional Budget Office, 2007, “Research on the Comparative Effectiveness of Medical Treatments: Issues and Options for an Expanded Federal Role” , Washington, DC.

APPENDIX

This appendix provides greater detail on the SCORE statistical model discussed and used in Section 2.

Options for Appendix: 1) Describe in detail, or 2) Omit all together.

Table A Coefficients for Eq. (1)

		CHD		Non-CHD CVD	
		α	P	α	P
Low Risk	Men	-22.1	4.71	-26.7	5.64
	Women	-29.8	6.36	-31.0	6.62
High Risk	Men	-21.0	4.62	-25.7	5.47
	Women	-28.7	6.23	-30.0	6.42

Table B Coefficients for Eq. (2)

	CHD	Non-CHD CVD
Current Smoker	0.71	0.63
Cholesterol (mmol/L)	0.24	0.02
Systolic Blood Pressure (mmHg)	0.018	0.022

		CHD		Non-CHD CVD	
		Men	Women	Men	Women
STEP 1					
$S_0(\text{age}) = \exp\{-(\exp(\alpha))(\text{age} - 20)^P\}$		0.997715262	0.999716565	0.99945652	0.9997933
$S_0(\text{age}) = \exp\{-(\exp(\alpha))(\text{age} - 20)^P\}$		0.994953179	0.999452864	0.99917148	0.9997154
$S_0(\text{age}+10) = \exp\{-(\exp(\alpha))(\text{age} - 10)^P\}$		0.991171836	0.998235009	0.99724984	0.9986126
$S_0(\text{age}+10) = \exp\{-(\exp(\alpha))(\text{age} - 10)^P\}$		0.981068315	0.996720037	0.99600946	0.998197
STEP 2					
$w = \beta_{\text{chol}}(\text{chol} - 6) + \beta_{\text{SBP}}(\text{SBP} - 120) + \beta_{\text{Smok}}(\text{current})$		-0.12	-0.12	0.4	0.4
STEP 3					
$S(\text{age}) = \exp\{S_0(\text{age})\}^{\exp(w)}$		2.422727704	2.427031855	4.44159667	4.4438287
$S(\text{age}) = \exp\{S_0(\text{age})\}^{\exp(w)}$		2.416799897	2.426464285	4.43970834	4.4433124
$S(\text{age}+10) = \exp\{S_0(\text{age}+)\}^{\exp(w)}$		2.408708128	2.423844777	4.42699906	4.4360082
$S(\text{age}+10) = \exp\{S_0(\text{age}+)\}^{\exp(w)}$		2.38722007	2.420590142	4.41881476	4.4332587
STEP 4					
$S_{10}(\text{age}) = S(\text{age}+10)/S(\text{age})$		0.994213309	0.998686841	0.99671343	0.9982401
$S_{10}(\text{age}) = S(\text{age}+10)/S(\text{age})$		0.987760746	0.997579135	0.99529393	0.9977373
STEP 5					
Risk ₁₀ = 1 - S ₁₀ (age)		0.005786691	0.001313159	0.00328657	0.0017599
Risk ₁₀ = 1 - S ₁₀ (age)		0.012239254	0.002420865	0.00470607	0.0022627
STEP 6					
CVDRisk ₁₀ (age) = [CHDRisk(age)] + [Non-CHDRisk(age)]		0.009073257	0.00307301		
CVDRisk ₁₀ (age) = [CHDRisk(age)] + [Non-CHDRisk(age)]		0.016945323	0.00468352		