Changes in the Characteristics of Approved New Drug Applications for Antihypertensives

by

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Submitted to the Engineering Systems Division
in Partial Fulfillment of the Requirements for the Degree of
Master of Science in Technology and Policy

at the

Massachusetts Institute of Technology

June 2007

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Abstract

In this thesis, the control of hypertension provides the backdrop for my effort to investigate how clinical trial design has evolved for antihypertensive drug submissions reviewed and approved by the Food and Drug Administration between 1988 and 2001. To do this, I have constructed and undertaken a preliminary analysis of a number of quantitative surrogate measures of complexity and scale, such as trial design, numbers of patients, treatment lengths, active drug comparators, number of indications pursued, number of indications approved, and approval times. In addition, I review how practice guidelines for the treatment of hypertension have changed with advancing clinical and biological knowledge. I attempt to investigate whether a link exists between the changing characteristics of clinical trials for antihypertensive therapies and the evolving guidelines for treating hypertension, promulgated by the Joint National Committee Report on the Detection, Evaluation, and Treatment of High Blood Pressure, (JNC), a committee assembled by the National Heart, Lung, and Blood Institute.

Although the number of New Drug Applications (NDAs) examined in the antihypertensive class is too small to permit rigorous statistical analyses, I am nonetheless able to observe a number of apparent trends within the set of NDA submissions for antihypertensives approved by the FDA. Specific trends I observe in support of increasing trial complexity include: 1) trial sizes increase over time as measured by patient enrollments per trial (*p-value* = 0.003); 2) clinical trial designs over time have included greater numbers of arms per trial (*p-value* = 0.022); and 3) the number of drug-drug interaction studies in antihypertensive NDAs has increased with time (*p-value* = 0.027). These trends offer preliminary support for the hypothesis that clinical trials associated with NDA applications for antihypertensives have become more complex over the last two decades.

The mechanisms responsible for the observed increase in complexity are less clear. Based on available information, I cannot determine if FDA guidance documents or informal correspondence were responsible for making antihypertensive clinical trials more complicated, or whether pharmaceutical companies introduced greater complexity into the trial design for commercial reasons. Furthermore, while I observe that FDA guidelines did not precisely track changes in JNC guidelines for treating hypertension, it is not clear whether the discrepancies are meaningful. Future research might attempt to identify more precisely the causes of increasing clinical trial complexity, and attempt to relate trial complexity to the cost of drug development more generally.

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Acknowledgments

Completing this thesis and course of study would not have been possible without the help, support, and guidance of my research advisor, Professor Ernst Berndt. I also owe a debt of gratitude to my colleague Hsiao-Lan (Sharon) Lin, whose advice and companionship helped make the effort enjoyable.

I appreciate the assistance of the members of the FDA/MIT research team, who helped make this thesis possible. From MIT: Dr. Frank Douglas, Mark Trusheim, Melissa Dere, Jean Kim, and Dr. Fabio Thiers. From FDA: Randall Lutter, Ilisa Bernstein, and Don Banks.

I would like to thank my parents Nicholas and Linda MacNeil, and my sisters Marcia and Laura MacNeil, for their love and moral support.

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Glossary

ACE inhibitor: An angiotensin-converting enzyme (ACE) inhibitor is a member of an antihypertensive drug subclass that interferes with the renin-angiotensin-aldosterone system by inhibiting the enzyme dipeptidase A, which is responsible for hydrolyzing the hormone angiotensin I into angiotensin II.

Action Package: a dossier held by the FDA that contains all information relevant to the agency's review of a New Drug Application (NDA) or Biologic License Application (BLA). In its electronic form, the Action Package is a set of PDF files containing scanned-in documents of FDA reviews, notes to the file, and memos of meetings.

active control trial: a type of clinical trial design that randomizes one group of patients to receive the new drug (the subject of the study) and another group of patients to receive an existing treatment or drug, as a means of comparing the effect of the new and existing therapies

ALLHAT: The Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT) was the largest antihypertensive trial and the second largest lipid-lowering trial and included large numbers of patients over age 65, women, African-Americans, and patients with diabetes, treated largely in community practice settings.

α-blocker: Alpha adrenegic receptor blockers, or α-blockers, make up an antihypertensive drug subclass that inhibits α_1-receptors on catecholamines in arterioles and venules, allowing the hormone norepinephrine to stimulate vasodilation, thereby lowering blood pressure.

angiotensin II: A hormone derived from renin, which is produced in the liver. Angiotensin II acts to increase blood pressure by constricting arterioles and prompting the release of aldosterone, a hormone that simulates the kidneys to retain more salt and water in the bloodstream.

antianginal: used or tending to prevent or relieve angina pectoris, a disease characterized by paroxysmal attacks of substernal pain of short duration

antiarrhythmic: counteracting or preventing cardiac arrhythmia, an alteration in the rhythm of the heartbeat either in time or force that is of functional or organic origin

arm: An arm of a trial is any discrete group of patients randomized at the beginning of the study to undergo treatment different from the other randomized groups.

β-blocker: A beta adrenergic receptor blocker, or β-blocker, is a member of an antihypertensive drug subclass that inhibits the stimulation of renin production by interfering with the beta adrenoceptors on catecholamines.

bioavailability: the degree and rate at which a substance (as a drug) is absorbed into a living system or is made available at the site of physiological activity

BLA: A Biologic License Application (BLA) must be submitted to the FDA for pre-market approval of biologic therapeutics, as defined by the Public Health Service Act.

BMI: Body Mass Index

calcium channel blocker: a subclass of antihypertensive drug that inhibits the transport of Ca^{2+} into the cytoplasm of arterial smooth muscle cells

catecholamine: a class of neurotransmitters involved in the sympathetic nervous system.

diastolic blood pressure: the blood pressure in the body measured during the period just before the heart begins to contract again (known as diastole)

diuretic: a subclass of antihypertensive drug that promotes the body's excretion of water, either via: 1) the excretion of sodium and chloride in the urine (thiazide diuretic); 2) inhibiting the kidney's ability to reabsorb sodium, thus enhancing the loss of sodium in the urine (loop diuretic); or 3) blocking the exchange of sodium for potassium, resulting in excretion of sodium and potassium but relatively little loss of potassium (potassium sparing diuretic)

Division File System (DFS): an electronic file system used by the FDA's Center for Drug Evaluation and Research (CDER) to manage and distribute internal documents

drug-drug interaction: To determine whether an investigational new drug has the potential to interfere with the body's ability to metabolize or excrete other drugs that a patient may be taking concurrently, the FDA often requires that sponsors undertake drug-drug interaction studies.

epinephrine: the principal blood-pressure-raising hormone of the medulla of the adrenal glands, prepared from adrenal extracts and also synthetically, and used chiefly as a heart stimulant, as a vasoconstrictor in controlling hemorrhages of the skin and in prolonging the effects of local anesthetics

equivalence trial: a clinical trial design in which patients are randomized into arms comparing a new and existing drug in an attempt to establish that the new drug is neither worse than nor better than the existing therapy

FDA guidance: Guidance documents represent the Food and Drug Administration's current thinking on a particular subject. An alternative approach may be used if such approach satisfies the requirements of the applicable statute or regulations.

inclusion/exclusion criteria: The medical or social standards determining whether a person may or may not be allowed to enter a clinical trial. These criteria are based on such factors as age, gender, the type and stage of a disease, previous treatment history, and other medical conditions.

JNC: Joint National Committee on the Detection, Evaluation, and Treatment of High Blood Pressure. The committee came into existence as an offshoot of the National High Blood Pressure Education Program (NHBPEP), a program established by the National Heart, Lung, and Blood Institute in 1972 to increase "awareness, prevention, treatment, and control of hypertension." The JNC committee consisted of representatives from most of the major medical organizations, a broad array of academic medical researchers, and officials from other Federal agencies with public health responsibilities.

labile hypertension: Labile hypertension is blood pressure that fluctuates abruptly and repeatedly, often causing symptoms such as headache or ringing in the ears.

Medical Review: a review of a New Drug Application (NDA) performed by qualified personnel at FDA for the purpose of critiquing trial design and conduct, summarizing and critiquing applicant's analyses, selectively verifying applicant's findings, summarizing risks and benefits, and making a recommendation as to whether the NDA should be approved

NDA: a New Drug Application (NDA) is the vehicle through which drug sponsors formally propose that the FDA approve a new pharmaceutical for sale and marketing in the US. The documentation required in an NDA is supposed to tell the drug's whole story, including what happened during the clinical tests, what the ingredients of the drug are, the results of the animal studies, how the drug behaves in the body, and how it is manufactured, processed and packaged.

new molecular entity (NME): refers to a drug that contains no active moiety that has been approved by FDA in any other application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act.

norepinephrine: a hormone that occurs with epinephrine, has a strong vasoconstrictor action, and mediates transmission of sympathetic nerve impulses. However, it lacks or exhibits weakly most other epinephrine effects (as on cardiac output or blood-sugar concentration)

ouabain: an endogenous hormone synthesized in the adrenal gland

phase I trial: initial studies to determine the metabolism and pharmacologic actions of drugs in humans, the side effects associated with increasing doses, and to gain early evidence of effectiveness; may include healthy participants and/or patients

phase II trial: controlled clinical studies conducted to evaluate the effectiveness of the drug for a particular indication or indications in patients with the disease or condition under study and to determine the common short-term side effects and risks

phase III trial: expanded controlled and uncontrolled trials after preliminary evidence suggesting effectiveness of the drug has been obtained, and are intended to gather additional information to evaluate the overall benefit-risk relationship of the drug and provide and adequate basis for physician labeling

pivotal trials: the set of phase III trials that the FDA considers most significant for determining whether the sponsor has demonstrated that the study drug is safe and effective

placebo controlled trial: A method of investigation of drugs in which an inactive substance (the placebo) is given to one group of participants, while the drug being tested is given to another group. The results obtained in the two groups are then compared to see if the investigational treatment is more effective in treating the condition.

primary endpoint: the most important overall outcome that the clinical trial protocol is designed to evaluate

randomized trial: A study in which participants are randomly (i.e., by chance) assigned to one of two or more treatment arms of a clinical trial.

renin: a proteolytic enzyme that is found in the kidney and that leads to the production of the hormone angiotensin II

renin-angiotensin-aldosterone system: a biochemical pathway closely associated with the pathophysiology of hypertension because it can increase cardiac output and total peripheral vascular resistance

secondary endpoint: other outcomes (of secondary importance to the primary endpoint) that contribute to the interpretation of a clinical trial

stepped-care regimen: a course of treatment that starts with the drugs of lowest toxicity and adds drugs from other groups as needed. This permits the use of less toxic agents in mild and responsive cases, with the more powerful (and toxic) agents reserved for use in severe disease.

sphygmomanometer: an inflatable cuff attached to a device for measuring a patient's blood pressure

Statistical Review: a review performed by qualified FDA statisticians to evaluate the statistical relevance of the data in the NDA, with the main tasks of evaluating the methods used to conduct studies and the various methods used to analyze the data. The purpose of these evaluations is to give the medical officers a better idea of the power of the findings to be extrapolated to the larger patient population.

sympathetic nervous system: a branch of the autonomic nervous system that is always active at a basal level (called sympathetic tone) and becomes more active during times of stress. Its actions during the stress response comprise the fight-or-flight response.

systolic: the blood pressure in the body measured in the arteries during the heart's contraction (known as systole)

vasodilator: an agent (as a parasympathetic nerve fiber or a drug) that induces or initiates vasodilation, the widening of the lumen of blood vessels

Chapter 1: Introduction

1.1 Motivation and Objective

Studying the changing nature of clinical trial design has the potential to shed light on the much-publicized increases over time in the costs of drug development and the decline in R&D productivity of the pharmaceutical industry. One plausible explanation for a more expensive drug development process is that the complexity and scale of clinical trials have increased over the past 20 years. This thesis presents portions of one in a series of studies by a team of MIT students, MIT-HST faculty, and FDA officials examining the changing characteristics of New Drug Application (NDA) submissions reviewed and approved by the FDA in a number of therapeutic areas. Facilitated by a Memorandum of Understanding between the FDA and MIT, FDA Action Package Reviewers' summaries along with NDA publicly available data have been analyzed to explore what changes over time can be observed in the characteristics of clinical trials.

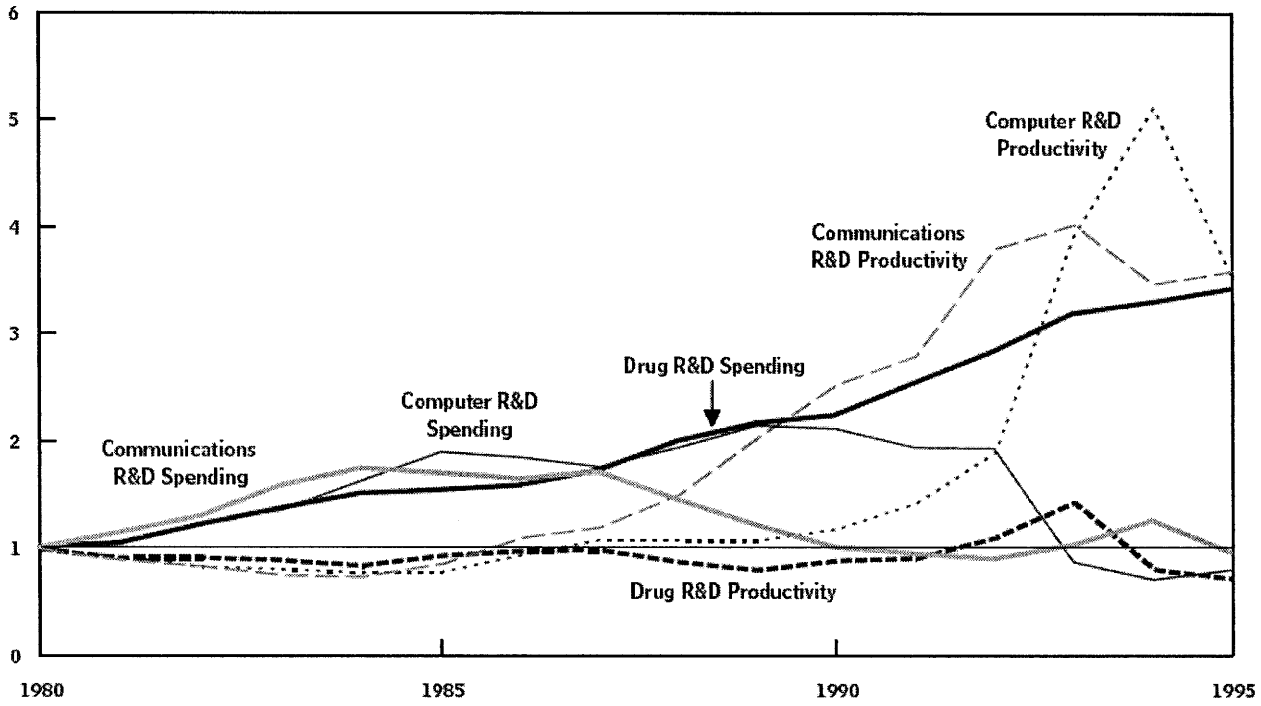
Learning about how clinical trials have changed over time could also lead to new insights into whether or to what extent clinical treatment guidelines are reflected in the design of clinical trials to assess the safety and efficacy of new drugs to treat a particular medical condition. This thesis describes how practice guidelines for the treatment of hypertension have changed with advancing clinical and biological knowledge. I attempt to investigate whether a link exists between the changing characteristics of clinical trials for antihypertensive therapies and the evolving guidelines for treating hypertension, promulgated by the Joint National Committee Report on the Detection, Evaluation, and Treatment of High Blood Pressure, (JNC), a committee assembled by the National Heart, Lung, and Blood Institute. To do this, I have constructed and undertaken a preliminary analysis of a number of quantitative surrogate measures of complexity and scale, such as trial design, numbers of patients, treatment lengths, active drug comparators, number of indications pursued, number of indications approved, and approval times.

1.2 Pharmaceutical Industry R&D Spending and Productivity

Before charging headlong into the changes in clinical trials for antihypertensives, to provide context I consider other potential causes for the increase in R&D spending by the pharmaceutical industry and the simultaneous trend toward declining productivity in terms of innovative new drugs.

First, it is clear the absolute value of R&D spending in the pharmaceutical sector is large. One widely cited estimate for the average cost of developing an innovative new drug puts the cost at more than $800 million, and the average time required to develop an innovative new drug at about 12 years.[1] One must be clear, of course, by what we mean by "average cost of developing an innovative new drug." Included in this estimate is the cost of all the failed drug compounds the pharmaceutical company, or drug sponsor, must go through before landing upon a compound that successfully reaches the market. In addition, a sponsor's actual expenditures make up only about half of the total estimated cost. This is because there is a financial cost to tying up capital in years-long drug development projects that earn no return unless and until the drug is able to reach the market (if the capital had not been tied up in testing the new drug, it could have been used to earn a higher return elsewhere). The opportunity cost of capital is particularly pronounced in the pharmaceutical industry given the 12 years, on average, required to develop a new drug.[2]

Figure 1: Research and Development Spending and Productivity for Various US Industries[3]
(Index, 1980 = 1.0)



As shown above in Figure 1, R&D spending on drugs has risen with respect to R&D spending in the communications and computing sectors, while drug R&D productivity has dropped in comparison to productivity in these two fields.* A report completed in October 2006 by the Congressional Budget Office (CBO) found several potential explanations for the estimated 7.4 percent rise (above inflation) in average R&D costs during the 1980s, and the 9.4 percent rise (above inflation) during the 1970s.[4]

As its first plausible explanation for the continuing growth in R&D costs for innovative new drugs, the CBO report describes the increase in the percentage of drug projects that fail in clinical trials. According to the FDA, the proportion of all new drugs entering phase I trials that ultimately gain approval has fallen to 8 percent from a historical average of about 14 percent.[5] The later these failures occur in the drug development process, the more significant the effect on the average cost of developing a successful therapeutic.

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* This figure measures productivity as the number of patents granted in an industry per dollar of research and development spending. R&D spending in one year is compared with successful patents two years later, reflecting the lag with which such spending leads to patent applications.

The CBO report also proposes that rising R&D costs could be attributed to the cost of performing clinical trials. According to an estimate by DiMasi *et al*, average clinical phase costs grew fivefold between 1987 and 2000, or at an average rate of more than 12 percent per year in real terms, due to increases in the size and duration of clinical trials.[6] The DiMasi *et al* study also estimates that the average number of people per trial grew by 7.5 percent annually, from about 2,300 in the 1980s to more than 5,600 by the early 2000s. In a separate study DiMasi found that the average length of the clinical trial phase increased by 27 percent over the 1980s and then declined by 4 percent over the 1990s.[7] The CBO report suggests that sponsors may be motivated to perform clinical trials for marketing and product differentiation purposes, by comparing their drug with a competitor's in addition to a placebo (for the purposes of approving an NDA, FDA requires only that sponsors establish that their new drug is safe and efficacious in comparison to a placebo). However, including a head-to-head comparison with a competitor's drug will often require a larger and more costly clinical trial because differences in efficacy will be less pronounced than just between the drug and placebo.

Another potential explanation for rising drug R&D costs could be pharmaceutical sponsors' heightened focus on developing drugs for chronic and degenerative diseases rather than acute illnesses. Such drugs, which are meant to be taken by patients for a long time, increase the potential for financial returns should the drug be approved, but in the short run drugs for chronic diseases are more expensive to test in clinical trials because they may take longer to show statistically meaningful results. Clinical trials for such drugs may also require more vigilant monitoring for long-term side effects, further boosting the cost of the studies.

In addition, the CBO report points to advances in basic research that may have boosted R&D costs in the short run, but not yet induced the desired upswing in output of innovative new drugs. Many researchers predicted that new technologies such as genomics and proteomics would uncover biological insights that would rapidly lead to new drugs; instead, scientists discovered that translating biological

understanding into improvements in the efficiency of drug discovery and development is not trivial. Such learning costs could be partly responsible for lowering research output and raising costs. Lastly, the CBO report cites the increase in universities' total royalty income on patents (much of which are biomedical in nature) as evidence that more pharmaceutical sponsors are having to pay for access to basic research findings that in previous years might have been in the public domain.[8]

The foregoing discussion of potential sources for the growth in R&D spending should provide the reader with an understanding of the context for the subject of this thesis. However, it is important to stress that this thesis does not attempt to link changes in the complexity of clinical trials with their impact on the cost of clinical trials. Such an investigation would require estimates of the marginal cost per patient, and marginal cost per arm of a study, among other factors. Obtaining the information necessary to formulate these estimates would be challenging, given its proprietary nature, and is beyond the bounds of the current Master's thesis. In other words, the research described in the thesis focuses only on what the results purport to say about whether clinical trials have become more complicated or not.

1.3 Thesis Organization

The outline of the thesis is as follows. In Chapter 2, I provide an overview of the etiology of hypertension, and describe how treatment guidelines for the disease have evolved over time — concurrently with the development of new antihypertensive drugs. Chapter 2 also includes a brief discussion of how ethnicity has played a role in guidelines for treating hypertension. In Chapter 3, I provide an overview of the drug development process and introduce several general principles of clinical trial design. In Chapter 4 I present my research methodology, in Chapters 5 and 6 I discuss and interpret the results of the research, and in Chapter 7 I lay out conclusions and limitations to the analysis. Lastly, in Chapter 8 I provide policy context and discussion.

Chapter 2: Hypertension

2.1 Definition of Hypertension

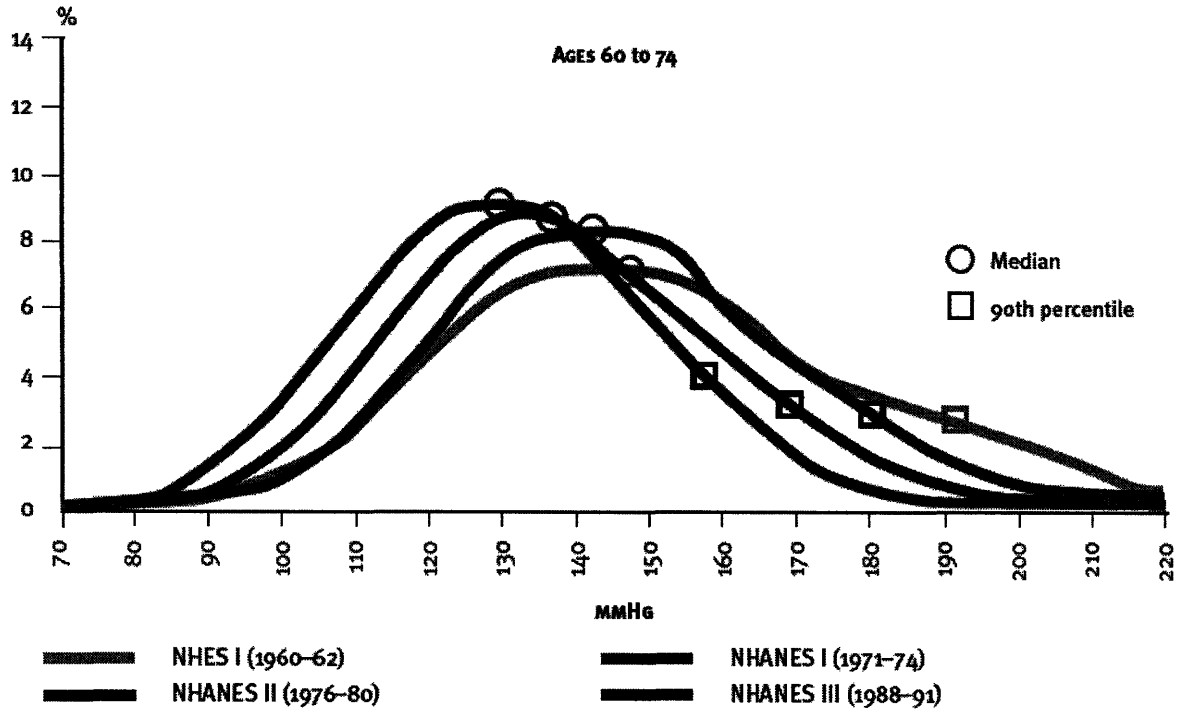
Hypertension, or abnormally high pressure in the arteries, is a condition common in the developed world and is becoming increasingly common in developing countries — in fact, about 20 percent of the world's adult population is estimated to be hypertensive.[9] Because hypertension has been shown to increase a patient's risk for cerebrovascular and ischemic heart disease,[10] the condition has attracted considerable interest from the medical community, particularly pharmaceutical companies, which have produced a steady supply of new treatments over the past few decades to help control high blood pressure. In this paper, the control of hypertension provides the backdrop for my effort to investigate how clinical trial design has evolved for antihypertensive drug submissions reviewed and approved by the Food and Drug Administration between 1988 and 2001.

2.2 Summary of Medical Condition (Hypertension)

In medical terms, hypertension is defined with the use of two measurements: systolic blood pressure and diastolic blood pressure. Using a sphygmomanometer (an inflatable cuff attached to a measurement device), healthcare providers measure the blood pressure in the arteries during the heart's contraction (known as systole), and also during the period just before the heart begins to contract again (known as diastole). Blood pressure is highest during systole, and lowest during diastole. Thus, when reporting a patient's blood pressure, physicians record the ratio of two values: systolic blood pressure over diastolic pressure. Normal blood pressure, as defined by the most recent JNC report, corresponds to a systolic blood pressure below 120 mm Hg, and a diastolic blood pressure below 80 mm Hg, or 120/80.

As shown in Figure 2, the last 40 years have seen median and 90th percentile blood pressures shift downward over time, according to data collected from a sequence of National Health and Nutrition

Figure 2: Smoothed Weighted Frequency Distribution, Median, and 90th Percentile of Systolic Blood Pressure for Ages 60-74 Years: United States, 1960-1991[11]



Examination Survey (NHANES) studies, a program of studies that combines interviews and physical examinations to assess the health and nutritional status of adults and children in the United States. Between the periods of 1976-1980 and 1999-2000, NHANES data show that the percentage of patients with hypertension receiving treatment has increased from 31 percent to 59 percent, and the percentage of people with high blood pressure controlled to below 140/90 mm Hg has increased from 10 percent to 34 percent.[12] Nonetheless, control rates for hypertension in the US are far from optimal.

With respect to etiology, the exact causes of hypertension are unclear. Heredity is a strong predisposing factor, and environmental factors such as obesity, a high-salt diet, and stress can exacerbate this predisposition. In a recent study investigating the effect of antihypertensive therapy on morbidity and mortality, Long *et al.* identified the following relative risk factors for hypertension: high body mass index (BMI), diabetes, family history, excessive alcohol use, high salt diet, exercise, race, age and sex.[13]

The body has several mechanisms for regulating blood pressure. The sympathetic nervous system, which controls internal body processes, can increase or decrease blood pressure by regulating the body's release of the hormones epinephrine and norepinephrine (a common example of when this occurs is during the fight-or-flight response). These hormones stimulate the heart to beat more rapidly and more powerfully, and for most arterioles to constrict, resulting in greater blood pressure. The sympathetic nervous system can also prompt the kidneys to eliminate less salt and water from the bloodstream, with the resulting increase in blood volume leading to higher blood pressure.

The kidneys also act separately to help regulate blood pressure. In addition to controlling the amount of salt and water excreted from the blood stream, which affects blood volume, the kidneys can increase blood pressure by releasing the enzyme renin, which leads to the body's production of the hormone angiotensin II. This hormone acts to increase blood pressure by constricting arterioles and prompting the release of aldosterone, a hormone that stimulates the kidneys to retain more salt and water in the bloodstream. This biochemical mechanism, known as the renin-angiotensin-aldosterone system, is closely associated with the pathophysiology of hypertension because it can increase cardiac output and total peripheral vascular resistance.[14]

Another biochemical mechanism involving the intracellular sodium pump has been hypothesized to explain the etiology of hypertension in some patients. There is evidence that endogenous ouabain, an adrenal steroid, interacts with the $\alpha 2$ isoform of the sodium pump in vascular muscle cells to inhibit the pump's function, thereby inducing the Na/Ca exchanger to push more Ca^{2+} into the cytoplasm of vascular muscular tissue. Higher levels of intracellular Ca^{2+} increases the tone and contractility of smooth vascular muscle, leading to a rise in peripheral vascular resistance and higher blood pressure.[15]

While the causes of hypertension are still a matter of debate, the implications of the condition are known and fairly well defined. According to the 17th edition of *The Merck Manual*, "An untreated hypertensive is at great risk of disabling or fatal left ventricular failure, MI [myocardial infarction],

cerebral hemorrhage or infarction, or renal failure at an early age." Hypertension is also an important risk factor predisposing patients to stroke, and is one of three risk factors (including cigarette smoke and hypercholesterolemia) associated with increased incidence of coronary atherosclerosis. There is preliminary evidence that certain types of antihypertensive therapy can increase a patient's risk for diabetes,[16] but the more generally accepted phenomenon is of diabetes and hypertension acting in concert to increase a patient's risk for cardiovascular disease.[17] Medical treatment can prevent or forestall these eventualities; nevertheless, coronary artery disease is the most common cause of death for treated hypertensive patients.[18]

2.3 Treatment of Hypertension Prior to JNC IV

Up until the mid to late 1940s, many in the medical profession were confused as to the significance of high blood pressure. While some physicians realized the potential for later complications in patients, others saw hypertension as relatively benign. For example, the 1946 edition of Tice's *Practice of Medicine* states that "Overzealous attempts to lower the pressure may often do no good and often do harm."[19] Partly this attitude stemmed from ignorance, and partly from a lack of means to adequately treat high blood pressure without causing significant side effects in the patient.

Beginning in the late 1940s and early 1950s, however, physicians began to acknowledge the link between hypertension and cardiovascular disease. For the most severe cases of hypertension physicians began prescribing low-sodium and low-fat diets, and experimenting with doses of ganglion-blocking agents, catecholamine depletors, and vasodilators. The relatively crude nature of these pharmaceuticals for treating high blood pressure limited their use to the most severe sufferers; patients with relatively mild forms of the disease were often told that complications were unavoidable.[20] In one example of the nature of antihypertensive therapy at the time, President Franklin Delano Roosevelt, whose blood pressure began to rise in 1937, was treated with phenobarbital (a sedative used to control epilepsy and anxiety), a low-fat, low-sodium diet, and rest. Over the next seven years he developed left ventricular

hypertrophy, congestive heart failure, multiple lacunar infarcts (nonthrombotic occlusion of small, deep cortical arteries), and renal failure, dying in 1945 of a cerebral hemorrhage at the age of 63.[21] As Cutler points out in *Your Money or Your Life,*[22] a 1948 pamphlet on treating hypertension recommended that hypertensive patients slow down, and take a rest around midday. The pamphlet, published by the US Public Health Service, also mentioned a few more drastic therapies for hypertension, including sympathectomy (severing of the nerves to blood vessels) and pyrogen therapy (inducing fever to lower blood pressure).[23]

After 1958, the advent of diuretics dramatically improved physicians' ability to manage difficult cases of hypertension. Later, the introduction of α- and β-blockers in the 1960s and 1970s led to the first large-scale clinical trials to investigate the impact of antihypertensive drugs on patients with milder cases of the condition, and to perform the first dose-response studies of these agents in patients. By the mid 1970s, physicians had begun experimenting with combinations of various antihypertensives that appeared to increase patient response and reduce side effects.[24] As shown in Table 1, from the 1940s through the 1980s the pace of new drug development was rapid.

Table 1: List of Available Antihypertensive Drugs from the 1930s through 1997[25]

1930s	Veratrum alkaloids
1940s	Thiocyanates
	Ganglion blocking agents
	Catecholamine depletors (*Rauwolfia* derivatives)
1950s	Vasodilators (Hydralazine)
	Peripheral sympathetic inhibitors (guanethidine)
	Monoamine oxidase inhibitors
	Diuretics
1960s	Central α_2-agonists (sympathetic nervous system inhibitors)
	β-Adrenergic inhibitors
1970	α-Adrenergic inhibitors
	α-β-Blockers
	Converting enzyme inhibitors
1980s	Calcium channel blockers
1990s	Angiotensin II (AT_1) receptor antagonists

Over the subsequent decades, the Joint National Committee (JNC) on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure issued a series of reports summarizing the evolving

available scientific evidence, and offering physicians recommended practice guidelines. The content of this series of JNC reports is summarized in greater detail in Appendix I and Appendix II.

The first Joint National Committee report was designed to provide recommended treatment guidelines for physicians and their patients. The committee came into existence as an offshoot of the National High Blood Pressure Education Program (NHBPEP), a program established by the National Heart, Lung, and Blood Institute in 1972 to increase "awareness, prevention, treatment, and control of hypertension."[26] The JNC committee consisted of representatives from most of the major medical organizations, a broad array of academic medical researchers, and officials from other Federal agencies with public health responsibilities.

The first set of guidelines, issued in the 1977 report, recommended that patients with blood pressures >160/95 mm Hg have their blood pressure rechecked within a month, but patients over the age of 50 with this relatively mild degree of hypertension were to be left pretty much alone (at the time hypertension was considered to be relatively unimportant as a risk factor in that age group). This first JNC report also introduced the idea of a stepped-care regimen for patients suffering from severe hypertension, suggesting thiazide diuretics as a first line therapy, with catecholamine depletors (reserpine), methyldopa, or propranolol to be added if the patient did not respond. A third line of pharmacological attack included vasodilators (hydralazine), peripheral sympathetic inhibitors (guanethidine), or clonidine, an alpha 2 agonist.

The next two JNC reports (JNC II and JNC III), issued in 1980 and 1984, recommended thiazide diuretics and beta blockers as initial therapy, followed by second line therapies similar to that laid out in the first JNC report of 1977. By 1988, calcium channel blockers and ACE inhibitors had entered the marketplace (see Table 1), and the JNC IV report added those two classes of drugs as alternatives for initial therapy along with diuretics and beta blockers. Although there were no long-term morbidity or mortality outcome data associated with these two new classes of antihypertensives — they had not yet

been used in long-term clinical trials — it was clear that they were much better tolerated than earlier antihypertensive drugs such as guanethidine, methyldopa, and clonidine.

2.4 JNC IV to JNC VI

Up to and including the JNC IV report, issued in 1988, the decision to pursue antihypertensive treatment depended primarily on a patient's diastolic blood pressure (the measurement of pressure as the heart relaxes to allow the blood to flow into the heart). This preference was due partly to history — the earliest clinical trials showing the benefits of lowering blood pressure relied on diastolic measurements[27] — and partly due to an oversight in interpreting the literature. Of interest is a 1959 report in *Society of Actuaries* that indicated systolic blood pressure was a better predictor of health outcomes.[28] Compounding matters, reports in the literature state that the FDA used diastolic blood pressure as the basis for its criteria in assessing the efficacy of new antihypertensive medications,[29] at least until the agency issued new draft guidance in 2000. Today it is widely believed that diastolic blood pressure is a more potent cardiovascular risk for patients below 50 years of age, but above this age systolic hypertension is the more important factor.[30] There are no estimates of the cumulative impact on public health of past reliance on diastolic rather than systolic blood pressure to determine antihypertensive treatment, but physicians' focus on diastolic blood pressure as a target seems to have led to less than optimal control of hypertensives' blood pressure.[31]

Specifically, the JNC IV report focused on diastolic blood pressure as an intermediate end point; it referenced only five prospective, randomized, controlled trials of antihypertensive therapy with end points of morbidity and mortality, and one trial using congestive heart failure as an end point. (For descriptions of the major prospective clinical studies relevant to the recommendations in JNC IV through JNC VII, please see Appendix II). The JNC V report provided additional evidence from four clinical trials of antihypertensive therapy, pinpointing the effects of antihypertensives on a patient population with isolated systolic hypertension and a population with mixed systolic and diastolic hypertension. These

findings foreshadowed the later conclusion in the JNC VI report that systolic blood pressure (the pressure that blood exerts on the artery walls as the heart contracts to pump out the blood) is a better metric for treatment recommendations and goals.

By the time JNC issued its fourth report in 1988, the FDA had approved five of the six major classes of antihypertensive drugs that are still widely prescribed today, as shown in Table 2. On the basis of mechanism of action, however, each of these drug classes differs markedly from its peers. Diuretics act on the kidney to increase the amount of sodium eliminated from the bloodstream, thereby reducing overall blood volume and decreasing blood pressure. Some diuretics, such as indapamide and amiloride, also exhibit vasodilating effects. Beta adrenergic receptor blocking agents, or beta blockers, inhibit the stimulation of renin production by interfering with the beta adrenoceptors on catecholamines, a class of neurotransmitters involved in the sympathetic nervous system. Beta blockers have also been shown to reduce mortality in patients with heart failure (see Table 2). Alpha adrenergic receptor blockers, in contrast, inhibit α_1-receptors on catecholamines in arterioles and venules, allowing norepinephrine to stimulate vasodilation, thereby lowering blood pressure. Besides having antianginal and antiarrhythmic effects, calcium channel blockers also dilate peripheral arterioles by inhibiting the transport of Ca^{2+} into the cytoplasm of arterial smooth muscle cells. As mentioned earlier, higher intracellular Ca^{2+} concentrations increase the tone and contractility of vascular muscle tissue; thus calcium channel blockers act to reverse that effect. Angiotensin-converting enzyme (ACE) inhibitors interfere with the renin-angiotensin-aldosterone system by inhibiting the enzyme dipeptidase A, or angiotensin converting enzyme, which is responsible for hydrolyzing angiotensin I to angiotensin II. However, ACE inhibitors also stimulate the kallikrein-kinin system by inactivating the vasodilator bradykinin, blunting the blood-pressure lowering effect. Angiotensin II receptor blockers are more selective at interfering with the renin-angiotensin-aldosterone system because they do not interact with bradykinin.[32]

Table 2: Classes of antihypertensive therapy and factors affecting suitability for patients[33]

Class of drug	Compelling indications	Favourable effects on co-morbid conditions	Adverse effects on co-morbid conditions
Diuretics	Heart failure; isolated systolic hypertension	Osteoporosis	Gout; dyslipidaemia (high-dose diuretics)
β-Blockers	Myocardial infarction	Angina; essential tremor	Asthma; peripheral vascular disease; depression; secondary or tertiary heart block
Calcium antagonists	Isolated systolic hypertension	Angina; diabetes mellitus with proteinuria	Secondary or tertiary heart block
ACE inhibitors	Diabetes mellitus with proteinuria; heart failure; myocardial infarction	Renal insufficiency	Pregnancy; renovascular disease; hyperkalaemia
α-Blockers		Dyslipidaemia; prostatic hypertrophy; glucose intolerance	Orthostatic hypotension
Angiotensin receptor blockers		ACE inhibitor-induced cough	Pregnancy; renovascular disease; hyperkalaemia

ACE, angiotensin-converting enzyme.

After NHLBI released the JNC IV report in 1988, academic researchers began a series of three to five year studies to gauge the effects of diuretics as initial therapy and to compare diuretics to beta blockers. The results indicated that these treatments reduced cerebrovascular and cardiovascular morbidity and mortality.[34] It is interesting to note that these trials represent one of the first instances of employing a biomarker — reduction in blood pressure associated with antihypertensive treatment — as a surrogate endpoint for morbidity and mortality in clinical trials. Use of this biomarker was to some extent evidence-based: a meta-analysis of 12 antihypertensive clinical trials conducted before 1993 found that patients in the trials who received antihypertensive therapy experienced a 52 percent reduction in the occurrence of congestive heart failure compared to control or placebo subjects. Most of these trials used diuretics as initial therapy.[35]

On the basis of these findings, in its 1993 JNC V report, the JNC revised its recommendations suggesting that diuretics and beta blockers be the preferred initial treatment for hypertension, with calcium channel blockers, ACE inhibitors, alpha blockers, and alpha/beta blockers as possible alternative therapies, depending on the specifics of the patient's condition. The JNC V report upheld the view that combination therapy (at lower doses of each individual drug) could effectively lower blood pressure with

fewer side effects to the patient, but did not explicitly list recommended combinations. Rather, the JNC V report merely outlined multiple dosage forms of several individual agents.[36]

The JNC VI report, published in 1997, went much further than its previous two versions in providing a clinical rationale for selecting particular antihypertensive therapies. In addition to explicitly recommending that treatment decisions be based on systolic blood pressure, the report provided evidence for the benefits of diuretics and beta blockers — as well as calcium antagonists — for elderly patients with isolated systolic hypertension, and provided additional data showing a beneficial impact on congestive heart failure and systolic dysfunction. One study cited by the JNC VI report demonstrated the superiority of losartan potassium, a competitive antagonist of angiotensin II, over captopril, an ACE inhibitor, in terms of decrease in total deaths.[37] Another study indicated that a combined alpha/beta blocker, carvedilol, reduced morbidity and mortality in patients with congestive heart failure, especially in those with an ischemic basis.[38] A third study showed that adding dihydropyridine calcium antagonists to a regimen of diuretics and ACE inhibitors had beneficial effects on patients with heart failure.[39, 40]

JNC VI also provided more detailed information on the relative effects of certain classes of antihypertensives on patient populations with renal dysfunction. Until this report, the JNC had not been able to point to randomized, prospective, controlled clinical trial evidence to support recommendations on the relative advantages of certain classes of antihypertensives in subsets of hypertensive patients.[41] The report contained data indicating that ACE inhibitors were more beneficial than other agents for patients with type I and II diabetes mellitus and nondiabetic chronic renal failure, and that calcium antagonists also had renoprotective effects.[42]

Lastly, the JNC VI report recommended a more flexible treatment approach than either JNC IV or V. The JNC IV committee had advised physicians to take a stepped-care approach, adding other antihypertensive agents only if the patient did not respond to first-line therapy. JNC V elaborated on this theme, but maintained that diuretics and beta blockers should constitute the preferred method of

treatment. In the JNC VI report, however, the committee gave physicians greater leeway in devising individualized therapies, depending on a patient's comorbid conditions and special considerations. While still adhering to the established first line of defense — diuretics and beta blockers — the JNC VI report recognized that other classes of antihypertensives have greater benefits for patients with conditions such as diabetes mellitus and chronic renal insufficiency.[43] In part, this could reflect the fact that a wider and expanded set of patients were now being treated for hypertension.

2.5 JNC VI to JNC VII

One of the more noticeable amendments to treatment guidelines introduced in the 2003 JNC VII report, issued six years after JNC VI, is the inclusion of the new classification of a condition called "prehypertension" to describe adults with blood pressure ranging from 120 to 139 mm Hg systolic and/or 80 to 89 mm Hg diastolic. Previous reports had referred to "high-normal" blood pressure to describe the range 130 to 139 mm Hg systolic and 85 to 89 mm Hg diastolic (JNC III through VI), but the JNC VII brought out the new term in an attempt to focus physician's attention on these patients. (For a more thorough treatment of historical classification schemes for hypertension, please see Appendix I). While the committee did not recommend that these patients be prescribed antihypertensive drugs — maintaining a healthy lifestyle is described in the JNC VII report as the recommended treatment — the idea was to identify potentially hypertensive patients who might benefit from early intervention and to encourage physicians to be vigilant in monitoring these patients' blood pressure.

An additional change from JNC VI involved simplifying the classification of the various stages of hypertension. In the JNC VII report, NHLBI consolidated three stages of hypertension into two, grouping patients with systolic blood pressure above 160 mm Hg and diastolic blood pressure above 100 mm Hg with more severely hypertensive patients (≥179/110 mm Hg), as shown in Table 3. In previous reports, the committee had not explicitly stated that physicians should consider combination therapy for patients

with stage 2 hypertension (≥ 160/100 mm Hg); many providers considered these patients well-treated with just one antihypertensive agent.[44]

Table 3: Changes in Blood Pressure Classification, JNC VI to JNC VII[45, 46]

JNC 6 Category	SBP/DBP	JNC 7 Category
Optimal	<120/80	→ Normal
Normal	120–129/80–84	→ Prehypertension
Borderline	130–139/85–89	
Hypertension	≥140/90	→ Hypertension
Stage 1	140–159/90–99	→ Stage 1
Stage 2	160–179/100–109	→ Stage 2
Stage 3	≥180/110	

As to specific recommendations for antihypertensive drug treatments, the JNC VII report remained conservative in the face of pressure to confirm that newer classes of compounds were superior to diuretics (more recently approved classes of antihypertensives were thought to have blood pressure independent benefits for patients at risk of cardiovascular disease). An unexpected finding occurred in more recent trials, such as the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT). Results from this study showed that ACE inhibitors did not significantly reduce the risk of congestive heart failure when compared to diuretics. The general conclusion reached by the committee in the JNC VII report was that reducing cardiovascular morbidity and mortality rates is dependent on reducing blood pressure, and that most of the differences between drugs reported in the superiority trials reviewed by the JNC were in secondary endpoints, according to one analysis of the report.[47] Potential side effects represent one secondary basis for comparing the various classes of antihypertensive drugs; these are shown in Table 4.

Table 4: Common Side Effects of Antihypertensive Therapy Classes

Class of Antihypertensive	More common side effects	Less common side effects
Diuretics (loop)[48]	dizziness or lightheadedness when getting up from a seated position;	dryness of mouth; increased thirst; irregular heartbeat; blurred vision

Diuretics (aldosterone receptor blockers)[49]	none	abnormal vaginal bleeding; breast pain; chills; cloudy urine
Beta blockers[50]	decreased sexual ability; dizziness or lightheadedness; drowsiness (slight); trouble in sleeping	breathing difficulty and/or wheezing; cold hands and feet; mental depression; anxiety and/or nervousness; constipation
Calcium channel inhibitors[51]	drowsiness (flunarizine only); increased appetite and/or weight gain (flunarizine only)	breathing difficulty, coughing, or wheezing; irregular or pounding heartbeat; constipation; diarrhea
ACE inhibitors[52]	coughing (dry, continuing)	dizziness, lightheadedness, or fainting; skin rash, with or without itching, fever, or joint pain; diarrhea; headache;
angiotensin II receptor antagonists[53]	none	angioedema (rare)

Indeed, the ALLHAT study was particularly controversial in that it was unable to conclusively differentiate among a diuretic (chlorthalidone), a calcium-channel blocker (amlodipine), and an ACE inhibitor (lisinopril) on the basis of the primary end point of the study: risk of fatal coronary heart disease and nonfatal myocardial infarction. Nonetheless, the study authors (many of whom were also members of the JNC VII committee) concluded that diuretics were a preferred first line of defense for treating hypertension, because the ALLHAT results showed that amlodipine is less effective at preventing congestive heart failure, and that lisinopril is inferior to amlodipine and chlorthalidone in reducing patients' risk of stroke. Following the publication of the ALLHAT results, a debate ensued in the medical literature questioning the strength of the evidence supporting the superiority of diuretics, and some authors questioned whether cost (diuretics were long off-patent and therefore less costly than ACE inhibitors and calcium channel blockers) had played a role in determining that diuretics should be the first option for hypertensive patients.[54]

The JNC VII report also provided additional guidance on which classes of antihypertensive drugs were tied directly to reductions in mortality. Evidence showed that at least five classes of drugs reduced mortality — thiazide and thiazide-type diuretics, ACE inhibitors, angiotensin receptor blockers, β-

blockers, and calcium antagonists (both dihydropyridine and non-dihydropyridine) — α-blockers were noticeably absent from this list. Lastly, the report concluded that combination therapy (two to three drugs) was found necessary to reduce blood pressure in most patients to optimal levels, and provided guidelines to physicians for selecting the right combination given a patient's risk factors and comorbidities.[55]

2.6 Hypertension in African-Americans

High blood pressure occurs more often in African-Americans — 32 percent of blacks compared with 23 percent of whites and 23 percent in Mexican Americans.[56] In recent years evidence from clinical trials has suggested that black patients may respond differently to certain antihypertensive and heart failure treatments than other ethnic groups. The ALLHAT study in particular drew attention to the potential differences between self-identified black and nonblack patients in their response to diuretics and ACE inhibitors. Black patients who were randomized to ACE inhibitors had an increase of 5 mm Hg (systolic) and 2 mm Hg (diastolic) in average follow-up blood pressure, 40 percent higher risk of stroke, 30 percent higher risk of heart failure, 15 percent higher risk of combined coronary heart disease, and 19 percent higher risk of combined cardiovascular disease versus black patients randomized to receive the diuretic.[57] Although these differences were statistically significant, it is a matter of debate how much weight should be given these results when making recommendations for treating hypertension. For example, despite the greater sensitivity to diuretic versus ACE inhibitor therapy in black patients, the ALLHAT investigators concluded that physicians should prescribe diuretics as initial therapy irrespective of the patient's race. In other words, ACE inhibitors were considered secondary antihypertensive therapy for blacks, but also for whites, who did not show the same degree of sensitivity in their response to diuretics and ACE inhibitors.

The debate over the significance of putative differences in response to treatment across ethnic groups also has ramifications for clinical trial design. In practice, a properly designed clinical trial seeks

to strike a balance between the need to conduct a sufficiently rigorous test of efficacy (which would benefit from recruiting a narrowly-defined group of patients most likely to benefit from treatment) and the need to determine the generalizability of the therapy to routine medical practice (which would benefit from enrolling a broad range of patients). Thus, assessing the clinical benefits of a therapy targeting patients of a specific ethnic group can be challenging.

In the case of the vasodilator BiDil, for example, academic and commercial researchers wanted to show that the drug was effective in black patients, despite a lack of conclusive efficacy in a general trial that included patients from a broad range of ethnic groups. The African-American Heart Failure Trial (A-HeFT), the first heart failure trial in a self-identified all-black cohort, found that adding a fixed-dose combination of isosorbide dinitrate/hydralazine (BiDil) to standard neurohormonal blockade (treatment with α-blockers or β-blockers) gave patients a 43 percent improvement in survival, a 33 percent reduction in hospitalizations for heart failure, and a significant improvement in quality of life.[58]

Chapter 3: Clinical Trials

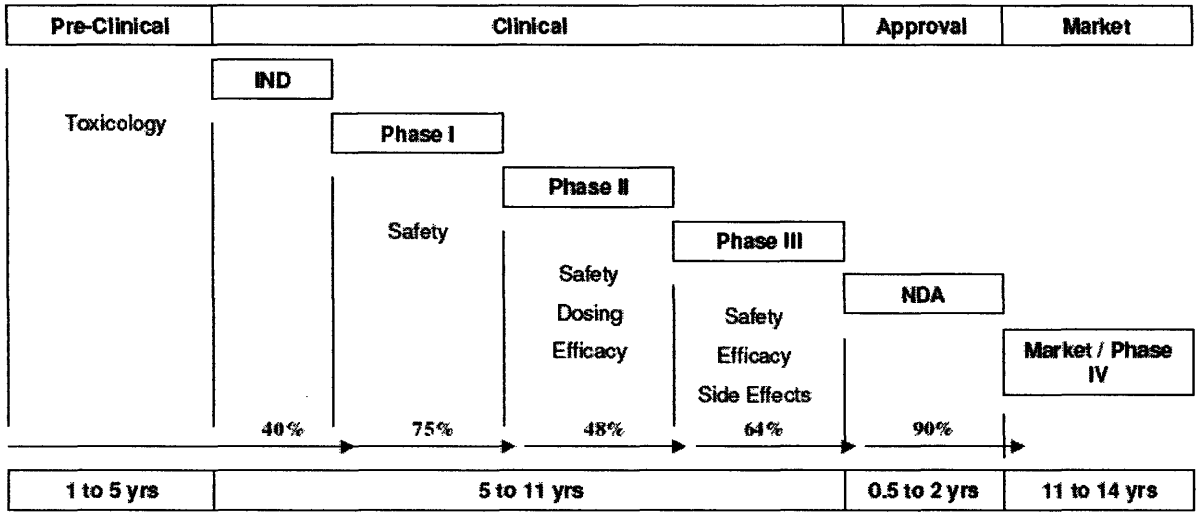
3.1 Attributes of Phase I-III Clinical Trials

Generally, a clinical trial is a planned experiment using human subjects designed to investigate the safety and efficacy of a course of treatment for patients with a given medical condition. One defining attribute of a clinical trial is that it relies on a limited sample of patients to make inferences about how to treat future patients with the medical condition in the general population. In other words, a clinical trial is designed to be prospective—to study how the patient sample will respond under the experimental design and protocol. In contrast, a retrospective study, which examines the outcomes of patients treated in a number of ways in the past, would not fall under the definition of a clinical trial. Retrospective surveys are far less powerful in determining the safety and efficacy of particular treatments, primarily because "unplanned observational studies contain serious potential biases (e.g. more intensive treatments

given to poorer prognosis patients may appear artificially inferior)..." as Pocock writes in *Clinical Trials: A Practical Approach.*[59]

As shown in Figure 3, clinical trials are often subdivided by phase of drug development. The focus of a phase I clinical trial is typically the safety, rather than efficacy, of the drug in human subjects. In pre-clinical studies, the pharmaceutical sponsor is likely to have tested the safety and non-toxic does of the drug compound in a mammalian system—most often mice or rats. Phase I clinical trials represent the first occasion the drug is tested in humans, or "first in man," to use industry parlance. In the past, healthy volunteers for phase I trials were often recruited from the prison population; today phase I volunteers are more likely to be graduate students enticed by the prospect of receiving a small fee in return for participating in the study.[60] A phase I clinical trial is often a dose-escalation experiment, which investigates the effect of giving participants increasing doses of the study drug according to a predetermined schedule. Phase I trials can also involve studies of drug metabolism and bioavailability. Overall, phase I studies typically require between 20 and 80 subjects and patients.[61]

Figure 3: Timeline and Components of New Drug Development[62]



Phase II clinical trials are also fairly small-scale experiments, but the purpose of these trials is broader, tending to investigate efficacy as well as safety and dosing. Typically, phase II trials involve no more than 100 to 200 unpaid volunteer patients with a defined medical condition, and require between

six months to two years to complete. Note that Figure 3 also includes estimates for the probability a given drug will successfully transition from one phase of the drug development process to the next.[63]

Phase III clinical trials, the primary subject of this thesis, are the most rigorous and extensive type of scientific clinical investigation of a new drug treatment. These trials investigate the safety and efficacy of a treatment in hundreds to several thousand patients with a specific medical condition, and can include studies of alternative formulations and doses of the drug. On average, the phase III process of drug evaluation lasts about four years, and an estimated 64 percent of drugs tested in phase III trials successfully make the transition into NDAs (New Drug Applications) or BLAs (Biologic License Applications).[64] The concept of a "pivotal" trial is also worth introducing here, as it refers to the phase III trials that are most significant for determining whether the sponsor has demonstrated that the study drug is safe and effective. Whether a phase III trial is pivotal is to some degree in the eye of the beholder; often the sponsor and FDA officials will disagree as to which phase III trials are actually pivotal. In the context of the research presented in this thesis, pivotal refers to which trials FDA officials have determined to be most significant for evaluating the safety and efficacy of the treatment.

3.2 Principles of Phase III Clinical Trial Design

A principle of a properly designed phase III clinical trial is that the study should be comparative, i.e. the response of a group of patients receiving the drug under investigation is compared to a group of patients receiving a placebo or standard treatment. Specifically, for a clinical trial to have statistical validity, the patients must be randomly assigned to each of the groups—or arms—of the trial. Thus, a randomized controlled trial is necessary to obtain an unbiased evaluation of the new treatment's potential value in the general population of patients. Properly designing a phase III clinical trial also requires that the sponsor develop and document the study protocol, which defines the exact type of patient to be included in the study, the treatments to be compared, and the methods for evaluating patients' response to treatment (the trial endpoints). As Pocock writes, the experimental protocol must address questions of:

1) size—"the trial must recruit enough patients to obtain a reasonably precise estimate of response on each treatment; and 2) avoidance of bias—the selection, ancillary care and evaluation of patients should not differ between treatments, so that the treatment comparison is not affected by factors unrelated to the treatments themselves."[65]

One element of trial design of particular relevance to the research presented in this thesis is the process for selecting patients to participate in a phase III clinical trial. In addition to ensuring that there are sufficient numbers of participants to create a study of sufficient statistical power, trial designers must establish strict criteria for which patients should be enrolled in the study. Defining these criteria involves balancing the need to assemble a sample population that may be identified as representative of a future class of patients to whom the trial's findings may be applied, with the need to assemble a sample population most likely to benefit from the new treatment under investigation (thereby more easily establishing the efficacy of the drug). In practice, trial designers use inclusion/exclusion criteria to find the range of patient characteristics most likely to straddle the middle ground between representativeness and specificity. An example of inclusion/exclusion criteria for patients in a trial of chemotherapy for advanced colorectal cancer as cited by Pocock is given in Appendix III.

Another attribute of clinical trial design to which the thesis refers extensively is the concept of trial arms. Typically a phase III pivotal trial is designed to randomize patients into one of at least two groups: those receiving the study drug and those receiving a placebo designed to appear indistinguishable from the study drug. Such a study is known as a placebo controlled trial. However, a placebo controlled trial need not only randomize patients into just two groups, or arms. If the trial is designed to also investigate the effect of varying the dose of the study drug, patients could be randomized into additional arms, with each arm receiving a different dose of the study drug. Alternatively, the purpose of a clinical trial could be to investigate whether a new drug is as efficacious as an existing drug. In this type of study, known as an active control trial, patients would be randomized

into an arm receiving the existing drug—the "active" comparator—and one or more arms receiving the study drug (or even an additional arm receiving a placebo). In a third type of trial—an equivalence trial—patients are randomized into arms comparing a new and existing drug in an attempt to establish that the new drug is neither worse than nor better than the existing therapy. This trial is most often employed when a sponsor is attempting to demonstrate the equivalence of a generic drug to its branded counterpart.[66]

Chapter 4: Research Methodology

4.1 Description of FDA Action Package

In order to determine who might benefit best from a particular antihypertensive therapy, someone — typically a pharmaceutical manufacturer — must develop the drug first. To gain FDA approval, a sponsor must usually submit data from at least two randomized clinical trials establishing safety and efficacy. These trials, which are often phase III trials, require on the order of hundreds of patients, and, in the case of antihypertensives, at least a year to complete. The past 15 to 20 years has seen sponsors face both regulatory and commercial challenges in designing trials and assembling the dossier of safety and efficacy data analysis needed to submit a New Drug Application (NDA).

Examining archival FDA data has provided quantitative insights into how clinical development for pharmaceuticals in general, and antihypertensives in particular, has changed over the past 15 years. This preliminary research has also helped generate several hypotheses concerning the importance of key factors in the changes observed over this time period. In this analysis I have focused on data from the primary studies cited by FDA Medical Officers as the basis for approval by the FDA. The primary documents for this quantitative assessment are the NDA reviews for new molecular entities with approval dates from 1991-2002, corresponding to submission dates between 1988 and 2001.

An NDA is divided into a number of different sections: non-clinical studies, including pharmacology, chemistry, and microbiology; clinical studies; integrated summaries of efficacy and safety;

labeling information; manufacturing details; and packaging information. For my purposes, the clinical data section, comprised of the Medical Officer's Review, the Statistical Review, and the Clinical Pharmacology Review, contained the most relevant data.

The primary data source, the Medical Officer's Review, is a comprehensive evaluation and assessment of safety and efficacy, with emphasis on what the FDA interprets as pivotal phase III trials (these may or may not be the same as those identified by the sponsor as pivotal). Secondary data sources, such as the Statistical Review and the Clinical Pharmacology Review, were useful for finding summaries of trial sizes and study design, as well as for information regarding special population and drug-drug interaction studies. Table 5, shown below, is a condensed version of the data collection sheet I used to assemble the information on each antihypertensive NDA relevant to my analysis of complexity.

Table 5: Information Captured from FDA Archives on Antihypertensives

NDA SUMMARY	PIVOTAL TRIAL SUMMARY
Drug Identification 1. NDA # 2. Generic Name 3. Brand Name 4. Sponsor Name 5. Therapeutic Class	Study Design 1. Study Name 2. Study Features
General Reviewing Information 1. FDA Reviewing Division 2. # of Review Cycles 3. Priority/Standard 4. Fast Track/Accelerated Subpart H 5. First in Class (Y/N) 6. Submission Date 7. Approval Date	Study Structure 1. Comparator 2. Dosages 3. Dose Frequency 4. Dose Duration 5. # of Patients Enrolled 6. # of Drop-Outs 7. Attrition (%)
Dosage 1. Route of Administration 2. Dosage Form 3. Dosage Strengths 4. Inpatient/Outpatient	Endpoints 1. Primary 2. Secondary
Safety 1. Black Box Warning at Approval 2. Black Box Warning Ever 3. # of Patients in Safety Database	# of Total Patients in Pivotal Trials

Study Summary 1. Indications a. Applied b. Approved 2. Special Studies a. Elderly (>65 yrs) b. Pediatric c. Cardiac d. Liver Insufficiency e. Renal Insufficiency 3. # of Pivotal Trials a. According to sponsor b. According to FDA 4. Total Studies in NDA 5. # of Drug/Drug Interaction Studies	
Post-Marketing Commitments 1. Safety 2. Clinical 3. Pediatric 4. Special Population Studies	

The FDA NDA reviews are electronically available from a variety of sources: the Drugs@FDA public website, CDER's Division File System (DFS), and through the FDA's Action Package archival system. The Drugs@FDA website is publicly available, but a considerable amount of relevant (proprietary) material is often redacted. Both the DFS database and the Action Package archival system include non-public information. The Drugs@FDA and DFS databases contain links to reviews, approval letters, and labeling information. However, some information is unavailable, including data on non-approved indications (only approved NDA indications are in the databases) and drugs that have subsequently been withdrawn from the marketplace.

Because the FDA electronic archival process began in the 1980s, the Action Package is the most useful data source for accessing a complete NDA. The Action Package, in its electronic form, is a set of PDF files containing scanned-in documents of FDA reviews, notes to the file, and memos of meetings. As shown in Table 6, the sample of antihypertensives approved between 1991 and 2002 is relatively comprehensive. Although there are some inconsistencies in data reporting across the 16 antihypertensive

NDAs, the relative completeness of the sample provides confidence that the observations likely reflect general trends.

Table 6: Antihypertensives submitted between 1988-2001

	Compound Name	Year of Submission	Year of Approval	Class of Antihypertensive	Number of Indications Approved
1	felodipine	1988	1991	Ca channel	1
2	torsemide	1991	1993	diuretic (loop)	2
3	perindopril	1991	1993	ACE inhibitor	1
4	spirapril	1991	1994	ACE inhibitor	1
5	moexipril	1992	1995	ACE inhibitor	1
6	carvedilol	1993	1995	beta blocker	1
7	nisoldipine	1993	1995	Ca channel	1
8	losartan	1993	1995	angio II recep	1
9	trandolapril	1994	1996	ACE inhibitor	1
10	valsartan	1995	1996	angio II recep	1
11	irbesartan	1996	1997	angio II recep	1
12	eprosartan	1996	1997	angio II recep	1
13	candesartan	1997	1998	angio II recep	1
14	telmisartan	1997	1998	angio II recep	1
15	olmesartan	2000	2002	angio II recep	1
16	eplerenone	2001	2002	diuretic (aldosterone receptor blocker)	1

4.2 Hypotheses

Before beginning the data collection and analysis, I constructed a set of hypotheses, built around the central question of whether clinical trials for all drug classes in the investigation have become more complex. For the purposes of antihypertensive NDAs, the relevant hypothesis is: 1) Clinical studies have become more complex, according to the order in which a drug in a class is submitted for approval.

In the context of this thesis, it is important to note that "complexity"[†] refers to characteristics of clinical trials for which I could obtain quantitative information and comparisons.

Chapter 5: Results and Discussion

[†] According to Merriam-Webster's Unabridged Online Dictionary, "complex," definition **2 a :** having many varied interrelated parts, patterns, or elements and consequently hard to understand fully <a *complex* camera with many attachments> <a *complex* industrial process> <*complex* tissue>

5.1 Summary of the Data

As an initial analytical exercise, I grouped the data by subclass of antihypertensive to determine the average values associated with each of the variables important to this study. As shown below in Table 7, given the absence of any obvious trends, after viewing the data through this perspective I concluded that subclass of antihypertensive therapy may not be the best way to explain the variation among the putative indicators for clinical trial complexity.

Table 7: Summary of NDA Data, Arranged by Average for each Drug Subclass, Except Beta Blockers

	diuretics	calcium channel blockers	ACE inhibitors	angiotensin II receptor antagonists
pivotal trial patients per approved indications	806.5	1690.5	884.7	1929.6
average # of patients per pivotal trial	276.6	258.2	243.1	382.1
average # pivotal trials per NDA	6.5	6.5	3.7	5.0
average # of arms per pivotal trial	4.3	4.0	4.9	4.6
average # of drug-drug interaction studies per NDA	7.0	6.0	4.0	7.1
average % patient drop outs from pivotal trials	6.8%	12.7%	15.3%	10.6%
average dose duration (in days)	73.2	46.5	70.6	58.2
average # of days to approval	604.5	959.0	781.0	445.7

While some subclasses of antihypertensives are generally older than others, submission dates for the subclasses of calcium channel blockers and diuretics span five and ten years, respectively, and are interspersed with NDA submissions of drugs in other subclasses, as was indicated in Table 6. Thus, it is possible that viewing the data in chronological order of NDA submission date may offer a more informative analytical framework than examining by subclass.

In the sections that follow I attempt to follow this approach. I begin with a discussion of the number of patients associated with the efficacy and safety databases, and investigate the number of

pivotal trials per NDA and the number of study arms in these pivotal trials. Variation in the number of drug-drug interaction studies offers another probe of clinical trial complexity; percentage of patient dropouts provides a glimpse into the relative importance of discontinuations in complicating clinical trial design. Data on time to approval offer some validation that FDA efforts to reduce review time have met with success. Lastly, differences in inclusion/exclusion criteria over time present additional insights into how clinical trial design has changed.

It is worth noting there are many possible metrics for clinical trial complexity for which I do not observe trends (data not shown). For example, by inspection I can determine that there was no trend over time for dose duration, defined as the number of days patients in the trial were given the active compound. Likewise, I do not observe any trend in the prevalence of combination, crossover, or multidose trials in antihypertensive NDAs over time. Combination trials, defined as clinical studies to investigate the combined antihypertensive effect of the study drug plus another therapy (usually the diuretic hydrochlorothiazide), appear primarily in supplementary NDAs, and only occasionally did I observe these trials in my sample of antihypertensive NDAs. Nor are there trends associated with the number of clinical trials deemed "pivotal" by the sponsor, even when this number is normalized by the number of pivotal trials deemed pivotal by the FDA.

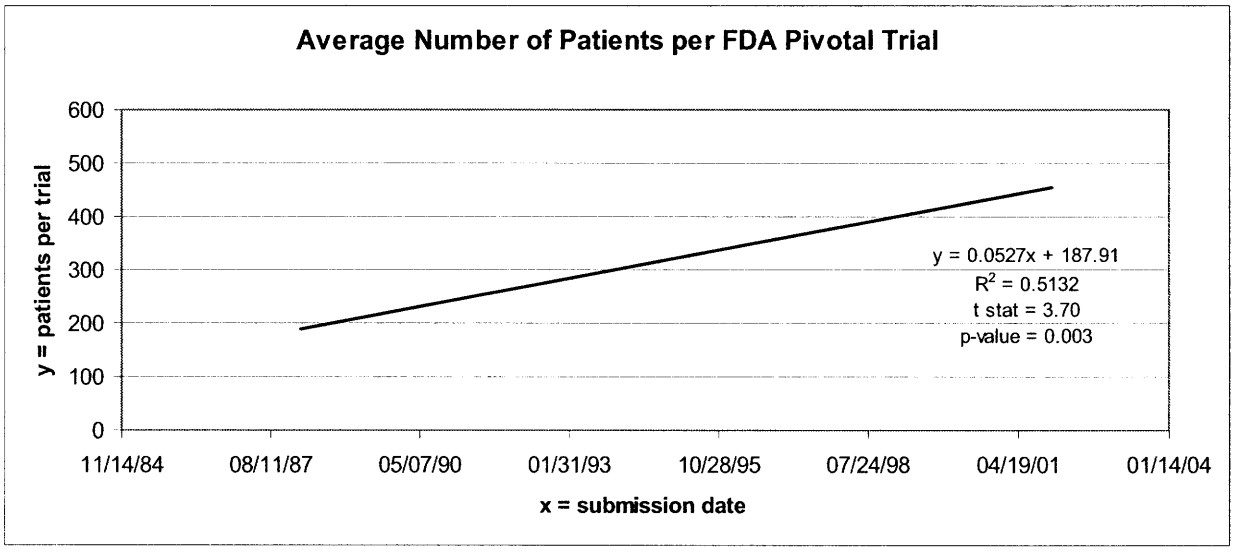
5.2 Increase in Patients per Pivotal Trial

A broad look at how the complexity of antihypertensive NDAs has changed with time can be obtained from examining the average number of patients per FDA pivotal trial as a function of submission date. Pivotal trial is a somewhat ambiguous term, given that the drug sponsor and FDA often differ in their determination of which trials are necessary to support the application. In this analysis I define pivotal trials as the set of studies that FDA reviewers deemed necessary and sufficient to support the drug's efficacy (pivotal trials were necessary but not sufficient to support a drug's safety, the latter entailing analysis of the entire safety database). For some NDAs, the Medical Review listed the trials that

FDA considered vital to supporting the application; in others, it was necessary to seek additional guidance and/or confirmation of the number of pivotal trials from the Statistical Review, which tended to elaborate on the validity of the trials under review.

It should be noted that there is no obvious trend associated with the *total* number of patients in a particular NDA per approved indication, but when the total is normalized by the number of trials deemed pivotal by FDA, the upward trend is visible, as shown below in Figure 4 (Note: individual data points have been removed because of FDA policy restricting the release of proprietary data). In a simple bivariate regression, the coefficient estimate on the explanatory variable of submission date‡ is positive and significant ($R^2 = 0.513$, *t statistic* = 3.70, *p-value* = 0.003). Between 1987 and 2001, the predicted number of patients per pivotal trial more than doubled, from about 200 to 450, an average annual growth rate of about 6.0 percent. Identifying the exact reasons underlying the increase in patients per trial is challenging,

Figure 4: Average Number of Patients per FDA Pivotal Trial



however, as there could be several explanations for this phenomenon. For example, the effect of the drug on blood pressure could be small, requiring a greater sample size to establish the validity of the drug's

‡ Microsoft Excel stores dates as sequential numbers which are called serial values. By default, January 1, 1900 is serial number 1, and January 1, 2008 is serial number 39448 because it is 39,447 days after January 1, 1900. To normalize the data, I set the first NDA submission date, February 26, 1988, equal to zero, and adjusted the other submission date values accordingly. The normalization allows me to present a more meaningful y-intercept value.

effectiveness (minimum effect size). Alternatively, a larger patient population may have been necessary due to changes in FDA guidelines for clinical trials, reflecting safety concerns. Another scenario could involve the sponsor adding comparator arms for commercial reasons, thereby requiring a greater number of patients to reach a statistically significant conclusion.

In an attempt to understand these complications, I generalized the linear least squares regression analysis to allow for differential relationships among NDAs in different drug classes. Because there are five classes of antihypertensive drugs embedded in the sample — diuretics, beta blockers, calcium channel blockers, ACE inhibitors, and angiotensin II receptor antagonists — I incorporated four dummy variables into the regression to explore any differential aspects involving the various drug classes. Specifically, I estimated a multivariate regression in which in addition to the submission date I added four class dummy variables, with the angiotensin II receptor antagonist class acting as the reference intercept term and the coefficients on the four dummy variables representing differential intercepts from the reference class. The results indicated that there were no significant differences among the five drug classes.§ Repeating the analysis with three dummy variables allowed me to combine beta blockers (n = 1) and diuretics (n = 2) into a single class, but again the regression results did not point to significant differential contributions from any of the four aggregated classes of antihypertensive drugs.**

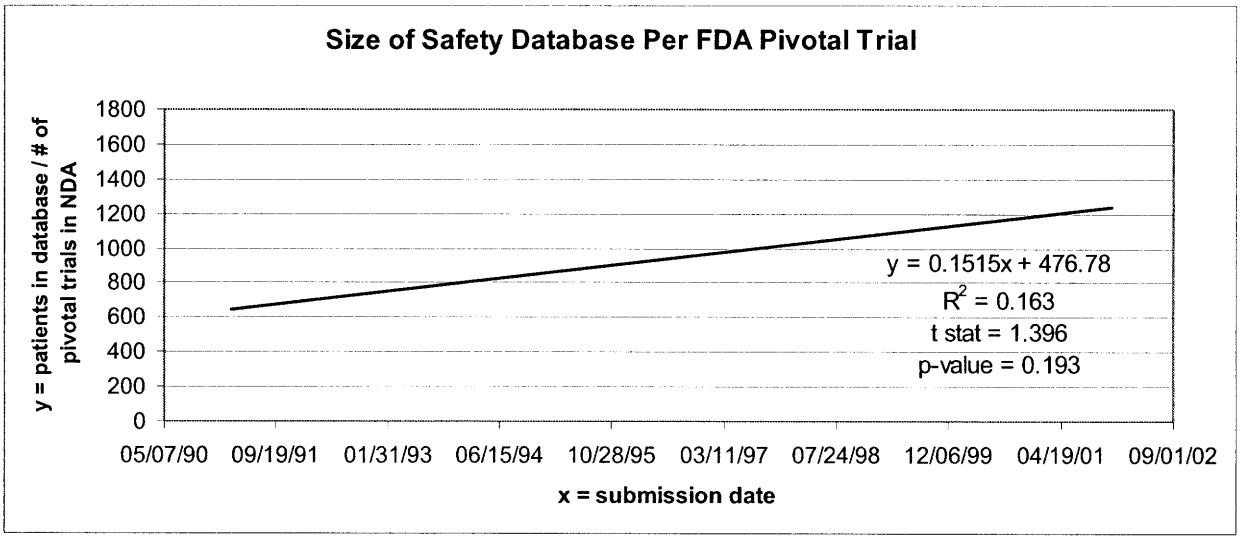
There is, however, some very weak evidence that the increase in average number of patients per pivotal trial reflects a greater investment on the part of sponsors in establishing drug safety and efficacy. With respect to the antihypertensive NDAs for which safety database information was available (n = 12), the average size of the safety database also increased with submission date, when normalized by the number of trials deemed pivotal by the FDA, as shown in Figure 5 ($R^2 = 0.163$, *t statistic* = 1.396, *p-value* =

§ While the value for R^2 increased to 0.688 as a result of incorporating the four dummy variables, none of the *t statistics* for the dummy variables had an absolute value greater than 1.771. The lowest *p-value* for the dummy variables was 0.110.

** Again, while the value for R^2 increased to 0.613 (from 0.513), the greatest absolute value associated with the *t statistics* for the dummy variables was 1.334, and the lowest *p-value* was 0.212.

0.193). Again, individual data points have been removed in order to comply with FDA policy on nondisclosure of proprietary data. Note that this trend is positive but not statistically significant, perhaps due partly to the further reduced sample size (only 12 out of the available 15 NDAs had reliable data on safety database size). Notably, however, over the eleven year period between 1990 and 2001, the estimated regression line predicts an approximate doubling in size of safety database per FDA pivotal trial, from slightly more than 600 in 1990 to about 1,200 in 2001, an average annual growth rate of 6.5 percent. Although discussion of efficacy and safety are beyond the scope of this report, it is conceivable that greater numbers of patients are required when the therapeutic has marginal benefit in terms of safety and efficacy.

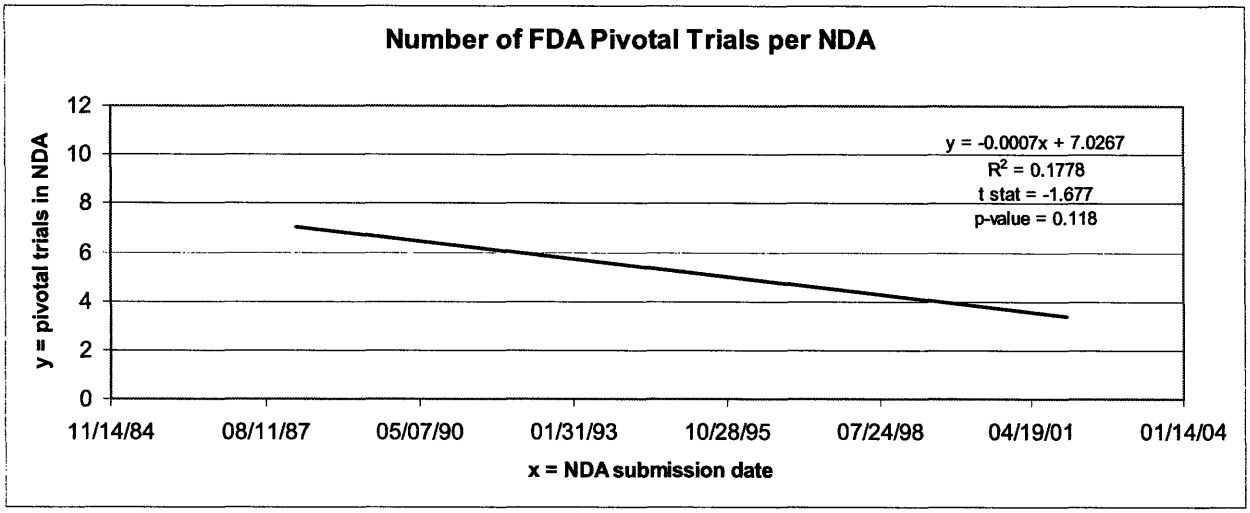
Figure 5: Size of Safety Database per FDA Pivotal Trial



5.3 Trends in Number of Pivotal Trials per NDA

Moving beyond the sheer number of patients involved in establishing efficacy and safety, I examined how the number of pivotal trials per NDA varied over time. As a first pass, I looked at all the hypertensives in the sample, and plotted the number of pivotal trials per NDA by submission date. I estimated a simple bivariate regression equation with the number of clinical trials as the dependent variable, and the NDA submission date as the explanatory variable. The result is shown in Figure 6. Given the variation in the data, there is fairly little in the way of a trend, but what trend does exist

Figure 6: Number of FDA Pivotal Trials per NDA



appears to show that the absolute number of pivotal trials per NDA has tended only modestly to decline over time, but not statistically significantly ($R^2 = 0.1778$, *t statistic* = -1.677, *p-value* = 0.118).†† The predicted number of FDA pivotal trials per NDA is about 3.5 in 2001, whereas in 1987 it is considerably larger at about 7.0.

5.4 Trends in Number of Arms per Pivotal Trial

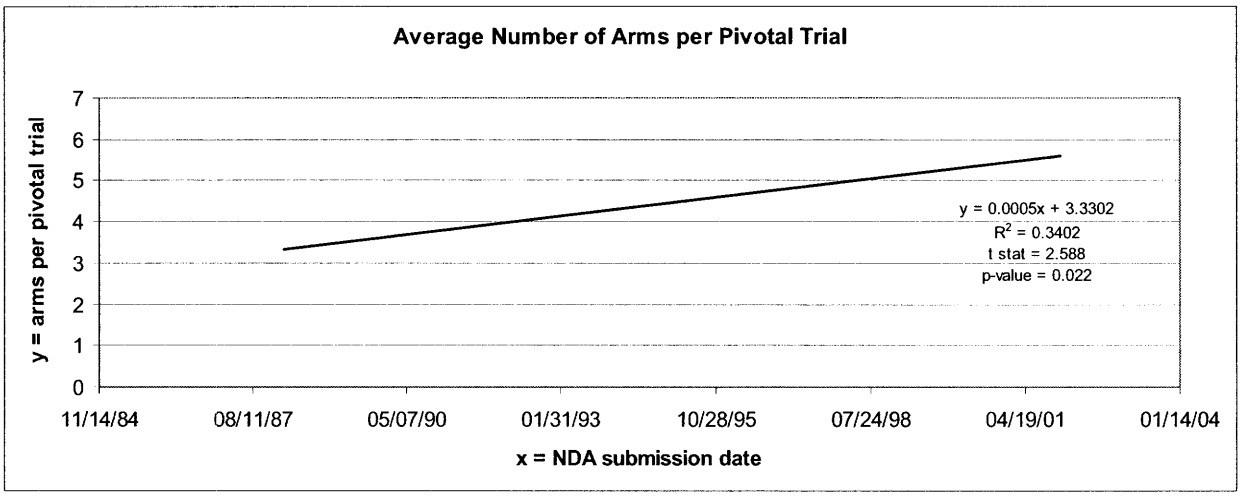
To help explain some of the trends described earlier, particularly the increase in average number of patients per pivotal trial, I investigated trends in the number of arms per pivotal trial. Data abstracted from the antihypertensive NDAs allows me to calculate an average number of arms per trial specified in each NDA.

Generally, an arm of a trial is any discrete group of patients randomized at the beginning of the study to undergo treatment different from the other randomized groups. Thus, a group of patients who received the study drug plus a diuretic would be an arm separate from a group of patients just receiving the study drug. Likewise, a group of patients randomized to receive 15 mg of the study drug per day over the course of an eight week study would be a different arm from a separate group of patients

†† I also estimated a bivariate regression equation for which the dependent variable was the ratio of pivotal to total number of clinical trials, (where total trials are defined to be the total number of clinical studies referenced in the NDA), with submission date as the explanatory variable. Although the coefficient estimate on submission date was positive, it was not significant (*p-value* = 0.364, $R^2 = 0.064$).

randomized to receive 25 mg per day of the study drug over the course of the clinical trial. On the other hand, a group participating in a titration study, which received one dose for a given number of weeks, and then a higher dose for following weeks, would be considered part of the same arm in the trial. Given this classification, I estimated a simple bivariate regression equation with average number of arms per pivotal trial as the dependent variable, and submission date as the explanatory variable. The results provide qualified support for an increase in complexity over time, as shown in Figure 7 ($R^2 = 0.340$, *t statistic* = 2.588, *p-value* = 0.022). The estimated regression line implies that while the average number of arms per FDA pivotal trial was about 3.3 in 1987, by 2001 it had increased to about 5.5, an approximately 67 percent increase.

Figure 7: Average Number of Arms per NDA by Submission Date



In order to ascribe this trend to greater complexity in clinical trial design with greater reliability, it is necessary to probe more deeply into the data. Regression analysis using dummy variables to represent the various classes of antihypertensives provides one avenue. Using a procedure identical to that described above for the number of patients per pivotal trial, I defined three dummy variables to classify the data on arms per trial according to: 1) diuretics + beta blockers; 2) calcium channel blockers; and 3) ACE inhibitors, with angiotensin II receptor antagonists as the reference class. The equation for the regression that results is given by:

$$y = 0.000717x_1 - 0.124x_2 + 1.084x_3 + 1.358x_4 + 2.273$$

where:

x_1 is the explanatory variable for submission date;

x_2 is the dummy variable for diuretics and beta blockers;

x_3 is the dummy variable for calcium channel blockers;

x_4 is the dummy variable for ACE inhibitors;

and the reference class consists of angiotensin II receptor antagonists.

The results indicate that the dummy variable for ACE inhibitors came closest to displaying a differential intercept relative to the reference class of angiotensin II receptor antagonists ($R^2 = 0.605$, *coefficient* = 1.358, *t statistic* = 2.253, *p-value* = 0.048).‡‡ Notably, in comparison to the simple bivariate regression, the coefficient estimate on x_1 (submission date) increased in this specification with differential intercepts, and became more significant ($R^2 = 0.605$, *coefficient* = 0.0007, *t statistic* = 3.544, *p-value* = 0.005).

Delving a little deeper into the data, I also identified the number of arms in each NDA devoted to comparators and combination therapy, rather than a placebo. Collecting this information was designed to help gauge how closely the number of arms in an NDA is tied to variations in dosing regimens, or to comparisons with competing drugs and combination therapy. In several NDAs the sponsor designed combination trials to gauge the relative antihypertensive effect of the study drug alone, versus the study drug taken in combination with the diuretic hydrochlorothiazide. (However, to gain FDA approval for the marketing of the study drug plus hydrochlorothiazide, the sponsor was required to submit a supplemental NDA). Total arms were then defined as the aggregate number of arms associated with the set of pivotal trials.

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‡‡ I also performed this analysis using four dummy variables to classify the data according to diuretics, beta blockers, calcium channel blockers, and ACE inhibitors, with angiotensin II receptor antagonists as the reference class. The analysis produced similar if slightly less significant results, showing that ACE inhibitors were best able to display a differential intercept relative to the reference class of angiotensin II receptor antagonists ($R^2 = 0.609$, *coefficient* = 1.382, *t* statistic = 2.167, *p-value* = 0.058). However, because there are only two diuretics and one beta blocker in our study, I thought it best to group diuretics and beta blockers, limiting the regression to three dummy variables.

While one could hypothesize that comparator arms might be more prevalent for follow-on drugs within a specific class, the data show otherwise. For example, the NDA submitted second in one antihypertensive subclass contained a total of seven comparator arms, compared with zero in the NDAs for the two members of that subclass submitted before and afterwards. Likewise, there does not appear to be any chronological significance to the prevalence of comparator arms for the angiotensin II receptor antagonists contained in the sample. NDAs corresponding to three members of a different antihypertensive subclass contained no comparator arms, whereas the first two from the class to be submitted contained three and five comparator arms, respectively. One possible interpretation is that complexity is greater for the first two entrants, because later entrants have learned from the predecessor compounds "what to do and not to do" in their development programs.

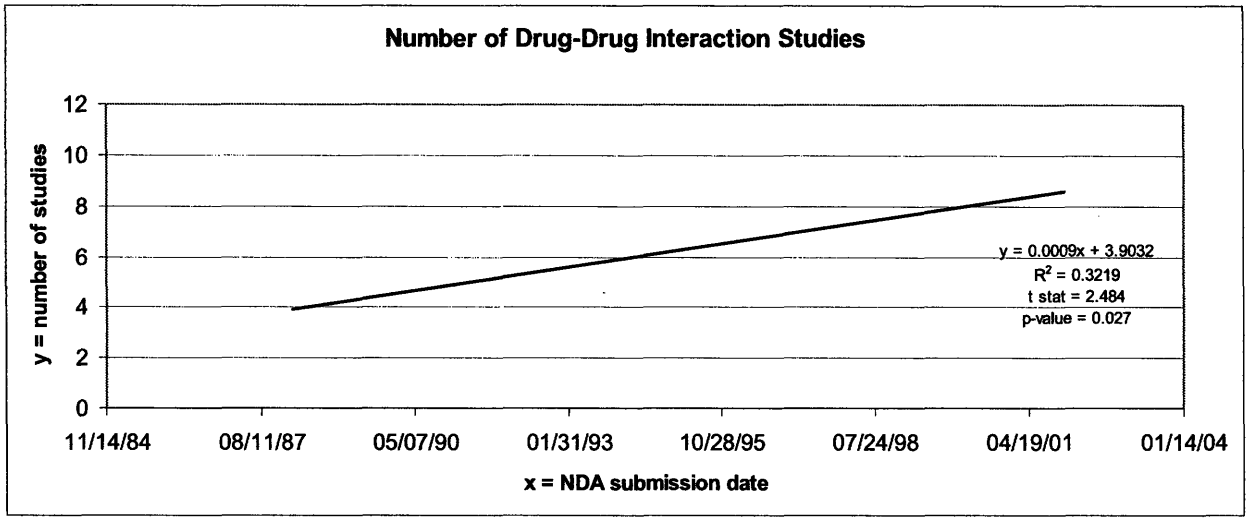
5.5 Increase in Drug-Drug Interaction Studies over Time

To determine whether an investigational new drug has the potential to interfere with the body's ability to metabolize or excrete other drugs that a patient may be taking concurrently, often the FDA requires that sponsors undertake drug-drug interaction studies. Of particular concern are drugs that either promote or interfere with the ability of cytochrome P450 enzymes (and N-acetyl and glucuronosyl transferases) in the liver to eliminate another active compound present in the patient's bloodstream.[67] For the antihypertensive drugs I studied, a typical drug-drug interaction study investigated the possibility of adverse drug reactions in patients receiving the study drug and another commonly prescribed medication such as digoxin, a treatment for congestive heart failure.[68]

With the data abstracted from the antihypertensive NDAs, I investigated how the prevalence of drug-drug interaction studies has changed over time. I estimated a bivariate regression equation with the number of drug-drug interaction studies as the dependent variable, and the submission date as the explanatory variable. As shown in Figure 8, the number of these studies per NDA trended upward over the 14 years under investigation, implying that sponsors were increasingly designing clinical trials to

provide evidence regarding possible adverse drug-drug interactions ($R^2 = 0.322$, *t statistic* = 2.484, *p-value* = 0.027). The estimated regression line implies that while the number of drug-drug interaction studies per approved NDA was about 4.0 in 1987, by 2001 this more than doubled to 8.5, an average annual growth rate of 5.5 percent.

Figure 8: Number of Drug-Drug Interaction Studies



Part of this increase could be due to increased awareness and understanding of the mechanisms through which a study drug can interact with other commonly prescribed medications. In the early 1990s the histamine H_1-receptor antagonist terfenadine (Seldane) became well-known for drug interactions that were uncovered only years after its initial approval in 1985. Because terfenadine was the first antihistamine that did not cause drowsiness, sales grew to over $600 million in 1995,[69] but the accumulation of evidence of occurrence of torsade de pointes (a variant of ventricular tachycardia) with drug-drug interactions involving terfenadine led to its withdrawal from the market in 1998. In fact, a report in *FDA Consumer* magazine cites the withdrawal of terfenadine, along with the drug interaction related withdrawals of the heart drug mibefradil (Posicor) in 1998, the antihistamine astemizole (Hismanal) in 1999, and the heartburn drug cisapride (Propulsid) in 2000, as contributing to a substantial increase in the number of drug-drug interaction studies submitted with NDAs to the FDA.[70] Notably, the JNC VII report, released in 2003, discusses the effect of common prescription and illegal drugs on blood

pressure, but does not specifically address the potential for drug-drug interactions. As there could be many explanations for why characteristics of NDAs (under the supervision of FDA) and JNC recommendations diverge, perhaps it is sufficient to say that the JNC recommendations placed a slightly lesser emphasis on the intricacies of pharmacology.

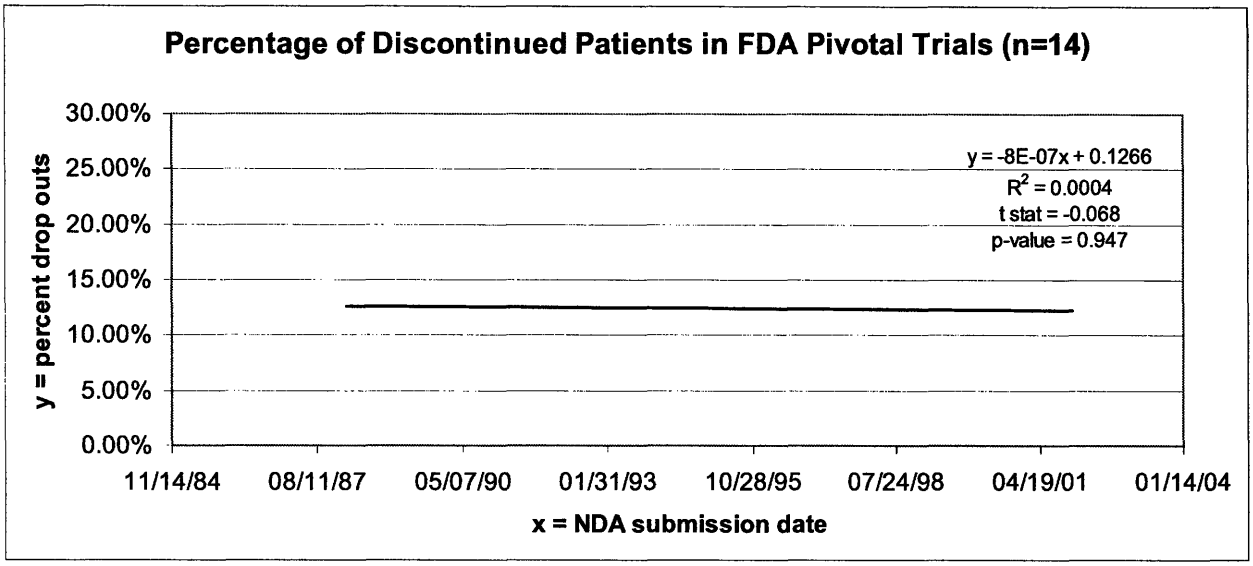
Other factors may also play into the overall trend toward more drug-drug interaction studies. In 1997 and 1999, FDA issued guidance to industry related to drug interaction studies, which may have encouraged sponsors to pay greater attention to these studies. The 1997 guidance document addressed the use of *in vitro* studies to examine potential drug interaction problems at an early state in the drug development process. Noting that advances in assay technology had made using human tissue and recombinant enzymes for drug-drug interaction studies easier, the guidance document promoted *in vitro* studies as an efficient means of uncovering adverse drug interactions that "often can reduce or eliminate the need for further clinical investigations."[71] In contrast, the 1999 guidance document suggests that sponsors' drug-drug interaction studies "explore whether an investigational agent is likely to significantly affect the metabolic elimination of drugs already in the marketplace and, conversely, whether drugs in the marketplace are likely to affect the metabolic elimination of the investigational drug."[72] Thus, as the number of medications on the market has grown over time, sponsors have encountered an increasingly significant burden to establish that the study drug does not adversely interact with other treatments likely to be taken the patient population.

5.6 Trends in Patient Drop-out Rates

Comparing patient trial discontinuation, or drop-out rates, across the antihypertensive NDAs presents another opportunity to assess empirically the hypothesis of increasing complexity. A general heuristic of drug development is that sponsors often seek to develop a drug in an already established class if the new compound has fewer or less onerous adverse side effects than drugs in that class already on the market. Because adverse side effects are often the cause of patients dropping out of a clinical study,

in theory it might be possible to track this phenomenon by examining the patient drop-out rate within a class of antihypertensives over time. The results of this analysis are shown below, in Figure 9.

Figure 9: Patient Drop-out Rates per NDA by Submission Date



As is apparent, there is no statistically significant trend with submission date as the sole explanatory variable ($R^2 = 0.0004$, t statistic = -0.068, *p-value* = 0.947). Additional regression analyses with dummy variables classifying for antihypertensive drug class indicated that none of these categories helped to explain the variation in patient drop-out percentage (all t statistics and *p-values* for the dummy intercept variables pointed toward insignificance). A separate analysis using one dummy variable representing first in class drugs and time as explanatory variables also did not produce statistically significant results.[§§] Lastly, I investigated whether a trend might emerge after dropping the first two data points, which appear to be gross outliers. While a simple bivariate regression analysis again pointed toward insignificance ($R^2 = 0.197$, t statistic = -1.566, *p-value* = 0.148), the statistics do noticeably improve.

In a later section (Chapter 6) I qualitatively examine changes over time in patient inclusion/exclusion criteria for pivotal clinical trials. One could imagine that changes in the stringency of

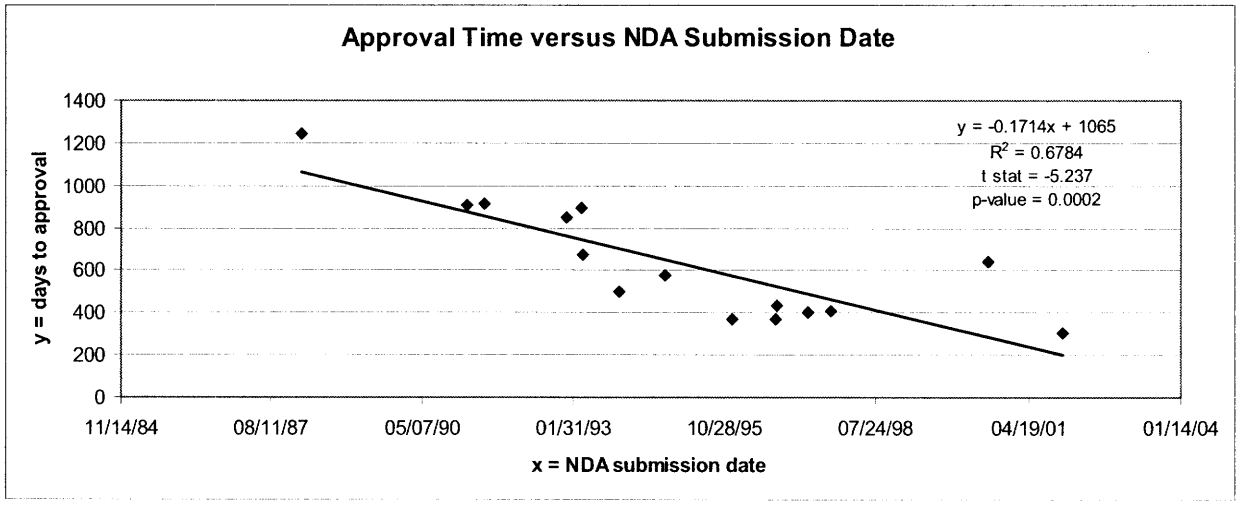
[§§] With submission date and a dummy variable for first in class drugs as explanatory variables, the value for R^2 in the regression analysis of patient drop out rates increased to 0.02. For submission date, values for the t statistic and *p-value* were -0.113 and 0.912, respectively; for the first in class dummy variable, values for the t statistic and *p-value* were -0.471 and 0.647, respectively.

inclusion/exclusion criteria might also have some bearing on patient drop-out rates. For example, if inclusion/exclusion criteria were to become less selective over time, a greater percentage of the participants in a clinical trial might be forced to drop out, for health or compliance reasons. As it turns out, the evidence suggests that several inclusion/exclusion criteria have become marginally more selective, such as screening out patients with greater than average body mass index or who recently participated in another clinical trial (please see Chapter 6 for more detailed discussion). It is unclear whether these more stringent criteria contributed to the variation in patient drop-out rates over time.

5.7 Decreasing Time to Approval

My analysis also found a marked trend with respect to the length of time required for FDA to review and approve an NDA (the sample is limited to NDAs eventually receiving FDA approval). As shown in Figure 10, the more recent the submission date, the more rapidly the FDA approved the NDA (R^2 = 0.678, *coefficient* = -0.171, *t statistic* = -5.237, *p-value* = 0.0002). The estimated regression line implies that while NDA review times in 1987 were about 1050 days (35 months), by 2001 this had fallen to about 200 days (6.7 months), an average annual decline about 11.2 percent. While it is possible that FDA

Figure 10: Days to FDA Approval for each Antihypertensive NDA as Function of Submission Date



reviewers were becoming more efficient at reviewing NDAs even while clinical trials were becoming more complex, a more likely explanation for this trend lies with the passage of the Prescription Drug User

Fee Act in 1992, which allowed FDA to boost its budget for NDA reviewers by charging sponsors fees associated with the submission and review of the application, and hiring more reviewers.[73, 74]

Chapter 6: Inclusion/Exclusion Criteria

Inclusion/exclusion criteria present another dimension to divine for trends with respect to NDA submission date and among the antihypertensive drug subclasses. The characteristics of trial patient populations are also potentially valuable as a means of probing the degree to which the trials reflect actual point-of-care delivery of antihypertensive therapeutics and/or changing JNC treatment guidelines. To investigate these potential relationships, I collected quantitative data on the inclusion/exclusion criteria for 14 of the 16 antihypertensives. I then set up a spreadsheet to summarize the similarities and differences in inclusion/exclusion criteria. Possible values for the fields were: 1) "yes" — the particular criterion is used in a trial; 2) "no" — the criterion is not applied to the trial; 3) "unclear" — it could not be determined from the NDA action package whether the trial applied the criterion; and 4) "n/a" — if the trial in question was in support of an indication other than the treatment of hypertension.

It is noteworthy that the inclusion/exclusion criteria for the 14 antihypertensives do not show a marked change in maximum or minimum diastolic blood pressure for inclusion in a study. The minimum diastolic blood pressure varied between 90 and 95 mm Hg, and the maximum varied between 110 and 115 mm Hg, but there was no discernible trend with respect to time or chronologically within subclass of antihypertensive therapy. Additionally, the blood pressure criteria were stated only in terms of diastolic blood pressure, not systolic blood pressure, apparently in accordance with FDA guidance prior to 2000, which recommended that sponsors rely on diastolic blood pressure as the basis for assessing the efficacy of new antihypertensive therapies.[75] (Previously, in 1997, the JNC VI report had recommended that all treatment decisions be based on systolic blood pressure.) It is apparent, however, that additional inclusion criteria were set within the angiotensin II receptor blockers to restrict for variations in blood

pressure in patients, and to identify and exclude patients whose blood pressure fluctuated significantly — a condition known as labile hypertension — during the placebo run-in period.

Two other observations emerge from this examination of inclusion/exclusion criteria. Within the subclasses of diuretics (n = 2) and ACE inhibitors (n = 3) there is a clear trend toward including restrictions on patients' weight in the more recently submitted NDAs. This criterion, expressed in terms of body mass index (patients whose weight exceeded a given variation from their ideal based on height), would presumably complicate the selection process as the percentage of obese Americans continues to rise. A further observation involves racial criteria. While most of the studies did not place any restrictions on the racial or ethnic make up of the patient population, there were three antihypertensive NDAs that did. One of the pivotal trials for an antihypertensive restricted enrollment to no more than 25 percent black patients, and another trial in the same NDA required that only non-black patients could enroll. Likewise, one of the trials for a different antihypertensive was restricted to "Caucasians only," and a trial for a third antihypertensive stipulated that study sites "were requested not to enroll more than 30 percent blacks."

One inclusion/exclusion criterion involved a restriction on patients who participated in a study of a different investigational drug in the 30 days prior to the antihypertensive trial. Within both the subcategories of ACE inhibitors (n=3) and angiotensin II receptor blockers (n=7), only the more recently filed NDAs contained this exclusion criterion. One might theorize that even while sponsors are increasing the average number of patients per pivotal trial, they are simultaneously making a greater effort to be selective to avoid contaminating the patient pool with those who have engaged in other studies of investigational drugs.

It is worth noting that of all the 81 studies in the sample encompassing these 14 NDAs, only two studies were not double-blinded. These two studies were included in NDAs submitted toward the beginning of the range of submission dates in the sample.

Chapter 7: Conclusion and Limitations

Although the number of NDAs examined in the antihypertensive class is too small to permit rigorous statistical analyses, I am nonetheless able to observe a number of apparent trends within the set of NDA submissions for antihypertensives approved by the FDA. Specific trends in the metrics I observe include:

- Trial sizes increase over time as measured by patient enrollments per trial (*p-value* = 0.003);
- Clinical trial designs over time have included greater numbers of arms per trial (*p-value* = 0.022);
- The number of drug-drug interaction studies in antihypertensive NDAs has increased with time (*p-value* = 0.027); and
- Inclusion/exclusion criteria for patients in trials have not changed greatly over time within subclasses of antihypertensives with respect to maximum and minimum blood pressure, but have tended to include greater restrictions over time on patient weight, as well as on the racial makeup of patient populations (qualitative analysis).

A number of potential metrics for complexity do not exhibit any trends over time, or when compared across the various subclasses of antihypertensive drugs. That said, however, increases in trial size, in number of arms per trials, and in number of drug-drug interaction studies offer preliminary support for the hypothesis that clinical trials associated with NDA applications for antihypertensives have become more complex over the last two decades, perhaps contributing to the increasing cost of drug development.

My analysis of the Medical Reviewers' summaries of 15 antihypertensives approved by the FDA since 1991 has revealed a number of tentative findings. I emphasize these findings are tentative for at least three reasons. First, the sample size of at most 15 is quite small, implying that it may be difficult to generalize from the trends I observed. Second, complete data were unavailable for one of the 16 antihypertensives approved by the FDA since February 1991. Lastly, it is important to emphasize that a

number of putative indicators of complexity did not exhibit any observable trends. The number of trials deemed pivotal by the sponsor, for example, did not increase with time; nor did I observe any increase in average dose duration for trials deemed pivotal by the FDA.

In spite of these limitations, I find that average trial sizes have increased over time as measured by patient enrollments per trial. While there could be many reasons for the greater number of patients associated with pivotal trials in antihypertensive NDAs over time, I conjecture that this may, at least in part, be due to sponsors' more thorough efforts to establish safety and efficacy. I observed other trends that support this supposition. Clinical trial designs over time have tended to include greater numbers of arms per trial; furthermore, the number of drug-drug interaction studies in antihypertensive NDAs has increased with time. Together these apparent trends offer preliminary support for the hypothesis that clinical trials in support of NDA applications for antihypertensives have become more complex over the last two decades.

Chapter 8: Policy Implications

8.1 FDA Guidance and JNC Treatment Recommendations

Given the lack of available information, it is impossible to know exactly what guidelines FDA had in place between 1988 and 2000 with respect to clinical trials for antihypertensives. Yet it is clear that JNC recommendations for the treatment of hypertension evolved over this time period. Should we be concerned that changes in JNC recommendations for treatment did not map directly on to changes in the inclusion/exclusion criteria for antihypertensive NDAs?

As one example, consider the 1997 JNC VI report's conclusions that systolic blood pressure (the pressure that blood exerts on the artery walls as the heart contracts to pump out the blood) is a preferable metric for hypertension treatment recommendations and goals than diastolic blood pressure (the measurement of pressure as the heart relaxes to allow the blood to flow into the heart). One might expect that given the JNC's conclusion, inclusion/exclusion criteria for trials submitted with NDAs after 1997

would state the acceptable range of hypertension for patients to be enrolled in terms of systolic blood pressure. Yet this is not the case. Instead, up to and including the last antihypertensive NDA, which was submitted in 2001, all inclusion/exclusion criteria for the acceptable range of hypertension were stated in terms of diastolic blood pressure. There just happens to be a simple explanation: according to literature reports, FDA used diastolic blood pressure as the basis for its criteria in assessing the efficacy of new antihypertensive medications.[76]

It is unclear whether FDA was right or wrong to use diastolic blood pressure to assess the efficacy of new antihypertensive drugs. There would be no harm in relying on diastolic blood pressure if an antihypertensive drug were equally effective at lowering diastolic and systolic blood pressure. The March 2000 ICH guidance document states, "Although all drugs to date have reduced both systolic and diastolic blood pressures, the recognition of isolated or predominant systolic hypertension as a significant and remediable risk factor demands explicit evaluation of the effect of a drug on systolic blood pressure."[77] Without further research to show that antihypertensives submitted between 1988 and 2000 were less effective because the inclusion/exclusion criteria were stated in terms of diastolic blood pressure, it appears that FDA's delay in updating its guidance was inconsequential.

Furthermore, from analyzing inclusion/exclusion criteria for the 15 antihypertensives submitted between 1988 and 2001, there is evidence to suggest that the minimum diastolic blood pressure for inclusion in a study did not stray from within JNC's definition of "mild hypertension," or what was later referred to as "stage 1" hypertension (see Appendix I for more details). For all 15 antihypertensives, the minimum diastolic pressure ranged between 90 mm Hg and 100 mm Hg, with the most common criterion being 95 mm Hg. By comparison, under JNC III and JNC IV, "mild hypertension" in terms of diastolic pressure was defined as 90-104 mm Hg, and under JNC V through JNC VII, "stage 1" hypertension referred to diastolic pressures of 90-99 mm Hg. One could argue that FDA should have been more vigilant in providing guidance directing sponsors to enroll patients with even the mildest form of

hypertension, as defined by the JNC. If FDA had done this, none of the observed inclusion/exclusion criteria would have defined the minimum diastolic blood pressure above 90 mm Hg. On the other hand, as all of the observed minimum criteria for diastolic blood pressure fall within the JNC's definitions for "mild" or "stage 1" hypertension, it is unclear if reducing the minimum diastolic pressure by 5-10 mm Hg would have been meaningful.

8.2 Is FDA Responsible for the Increasing Complexity of Clinical Trials?

My findings, though preliminary, suggest that important attributes of clinical trials for approved antihypertensives submitted between 1988 and 2001 have become more complex over time. Yet it would be desirable to relate the observed trends showing increasing complexity with data on the costs of clinical trials. This would allow one to gauge whether and to what extent these developments have contributed to the rising cost of drug development generally. Unfortunately, calculating the significance of such a contribution to drug R&D costs would require detailed knowledge of the accounting used for clinical trials. For example, I would need access to data on the marginal cost per patient in an average trial, and the marginal cost per arm of a study—proprietary data difficult to acquire in the context of a Master's thesis.

However, it may be appropriate to comment generally on some of the potential causes of the trends towards increasing complexity I observed for several characteristics of antihypertensive clinical trials. One question that has implications for regulatory policy is whether trials are becoming more complicated because of FDA requirements—*e.g.* guidance that would push pharmaceutical sponsors toward including more patients in pivotal clinical trials—or because of decisions the sponsors made independently for commercial reasons.

If it were true that FDA guidance served as a forcing function for changes in the characteristics of pivotal clinical trials, one could attempt to find confirmatory evidence by reviewing the FDA guidance for antihypertensive clinical trials in effect during the time period under investigation in this thesis, and

attempting to pick out how clinical trials may or may not have responded to changes in the underlying guidance. But there are two problems with this approach. First, only one of the two guidance documents in effect between 1988 and 2001 is available. The publicly-available guidance document, the most current guidance related to antihypertensive clinical trials, is a draft consensus principle signed in March 2000 by the International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH). The previous guidance document, entitled, "Clinical Evaluation of Antihypertensive Drugs" and in effect from May 1988 until March 2000, is not available via the FDA website or with the help of colleagues at the agency. The second problem with this approach is that only two of the fifteen antihypertensive NDAs in the sample were submitted after March 2000. In other words, even if the May 1988 document were available for review, it would be difficult to make a proper comparison between clinical trials submitted under the May 1988 guidance and those submitted under the March 2000 guidance.

It is possible that informal correspondence between FDA officials and representatives of the pharmaceutical sponsor could have been a conduit for FDA advice ultimately responsible for the observed increases in clinical trial complexity. Given the vague and general nature of the available FDA guidance document relevant to clinical trials for antihypertensives, consultations between company representatives and FDA officials—either over the phone, in writing, or in person—might be more valuable in determining how much of an impact on trial design could be tied to FDA consultations. Again, the problem is one of access to the necessary information. According to Dr. Frank Douglas, an advisor to this thesis, a sponsor likely maintains records of these interactions, but it is unclear to what extent FDA also records the details of every conversation with sponsors.

The other perspective on this issue is to attempt to find significant evidence of increasing complexity, the cause of which under no circumstances could be ascribed to FDA dictates or advice. For example, I conjectured that pharmaceutical sponsors seeking to market a drug within an already

established subclass of antihypertensive might be motivated for commercial reasons to compare its drug in clinical trials to the drugs of that subclass already on the market. If the clinical trial established that the new drug had advantages over the currently marketed therapy, the company might have a tool with which to differentiate its product and increase sales of its new drug. However, as described in Chapter 5, I did not observe any trends showing increasing frequency of comparator arms within antihypertensive subclasses over time.

Nonetheless, there are other explanations for the observations that would place responsibility for the increases in complexity in the hands of pharmaceutical sponsors. Two of the three statistically significant observations of increasing complexity—a trend toward more patients in pivotal trials over time and a trend toward more arms per trial over time—are not necessarily independent phenomena. In other words, an increase in the number of arms per pivotal trial over time might require that the overall number of patients involved in pivotal trials also increase over time. As discussed above, I did not find evidence that the number of arms per pivotal trial increased due to a tendency on the part of sponsors to include comparisons with competitors' drugs. However, this leaves open the possibility that the increase in arms per trial was instead due to greater emphasis on dosing comparisons in pivotal trials.

Why would sponsors tend to include more arms in pivotal trials for comparing effective doses of the study drug? It is plausible that sponsors, in an attempt to minimize the overall clinical timeline for drug development, were foregoing some phase II clinical trials (which are employed primarily for dose-response studies) and instead performing more extensive investigations of dose-response behavior in phase III trials. Decisions of this sort might push up the costs of clinical trials in the short run, as greater numbers of arms in a study would tend to require greater numbers of patients. Furthermore, phase III trials in general are an order of magnitude larger in patient population size than phase II trials. But in the long run, speeding up the drug's arrival on the market might result in financial returns for the sponsor

that would more than compensate for the additional development costs, particularly if the sponsor is in a race with a competitor to introduce a new therapeutic.

Lastly, the observed trends toward increasing complexity could stem merely from greater awareness on the part of pharmaceutical sponsors of the importance (from the perspective of liability) of thoroughly testing the safety and efficacy of clinical trials prior to FDA review. Because a drug for a chronic condition such as hypertension is designed to be taken by patients for many years, one imagines that a sponsor would want to establish and ensure that the drug be free of serious adverse effects. If not, the company could be open to substantial liability and loss of market share, not to mention damage to the company's reputation.

But for a moment let me leave aside the problem of identifying the actual causes of increasing complexity in clinical trials and instead assume, for the sake of argument, that pharmaceutical sponsors are complicating trial design and execution of their own volition, out of a sincere desire to thoroughly understand potential long term adverse effects on the patient population. From the perspective of public health, would it matter if pivotal clinical trials were becoming more complex? Or put another way; even if we assume the impulse to complicate clinical trials is motivated by beneficence, is this development in and of itself beneficial, or cause for concern?

One approach to considering this question is to ask who benefits, and who is harmed, when clinical trials become more complex over time. Addressing the latter first, if one assumes that increasingly complexity could be tied to increasing costs, then one could speculate that pharmaceutical sponsors suffer financially when clinical trials become more complicated. But as we noted above, a sponsor's investment in higher development costs might make sense financially if it contributed to getting the drug to market more rapidly. In broader terms, the cost of drug development is not very well correlated to the present value of future sales of the drug.[78] Instead, the price a pharmaceutical sponsor can charge for a new therapeutic is determined predominantly by the presence or absence of competitors' drugs for the

indication, and the real or perceived therapeutic benefit of the drug to the patient. Thus, higher development costs will not necessarily translate into a lower return on investment for the pharmaceutical sponsor (nor will lower development costs necessarily translate into a higher return). Given the lack of correlation between a pharmaceutical sponsor's spending on development and its return for any particular compound, it should follow that from the perspective of health care spending it is not clear whether lower drug development costs would lead society to spend less on drugs.

Thus, if it is not clear anyone or any organization suffers as a result of more complicated clinical trials, what is there to be concerned about? The issue is with the potential benefits. One might assume that a more complex clinical trial—such as one that involves greater numbers of patients or a greater number of arms—is necessarily providing greater insights into the safety profile and potential for causing adverse reactions in patients. But that would only be true if the drug under investigation in a clinical trial was meant to be prescribed in the real world for a relatively short length of time, similar to the dose duration in the study. If, as was the case with Vioxx, some adverse events only turn up after prolonged exposure to the drug in many patients, a more complicated clinical trial—unless it involved long-term monitoring and follow-up—would most likely not raise any warning flags.

The upshot is that for drugs designed to treat chronic conditions such as hypertension, complicating trials by including greater numbers of patients or arms may not cause much observable harm, but nor does this development necessarily impart any material patient benefit. Instead, one could argue that patients in general might be better served if pharmaceutical sponsors and the FDA shifted their increasing emphasis on phase III trials to greater phase IV post marketing surveillance, particularly for drugs meant to be taken for long periods of time. In this way, FDA could maintain the same threshold for approval on the basis of phase III pivotal trials, but increase the ability to detect adverse effects that might only become apparent after the drug is prescribed to orders of magnitude greater numbers of people and over greater lengths of time.

Appendix I: Summary of Blood Pressure Classification Schemes: JNC III through JNC VII

	JNC III (1984)[79]		JNC IV (1988)[80]		JNC V (1993)[81]		JNC VI (1997)[82]		JNC VII (2004)[83]	
	diastolic[9]	systolic[10]	diastolic	systolic[11]	diastolic	systolic	diastolic	systolic	diastolic	systolic
Optimal							<80	<120		
Normal	<85	<140	<85	<140	<85	<130	<85	<130	<80	<120
High normal	85-89		85-89		85-89	130-139	85-89	130-139		
Prehypertension									80-89	120-139
Mild hypertension	90-104		90-104							
Borderline isolated systolic hypertension		140-159		140-159						
Moderate hypertension	105-114		105-114							
Isolated systolic hypertension		≥160		≥160						
Stage 1					90-99	140-159	90-99	140-159	90-99	140-159
Stage 2					100-109	160-179	100-109	160-179	≥100	≥160
Stage 3					110-119	180-209	≥110	≥180		
Stage 4					≥120	≥210				
Severe hypertension	≥115		≥115							

[9] All blood pressures are stated in units of mm Hg.
[10] When diastolic bp is <90 mm Hg
[11] When diastolic bp is <90 mm Hg

Appendix II: Summary of Major Hypertension Therapy Clinical Studies (JNC IV-VII)

JNC Report Cited	Name of Study	Date findings published	Type of study	Details of population	Major findings
post-JNC VII	Second Australian National Blood Pressure Study (ANBP-2)[84]	2003	prospective, randomized, open-label study with blinded assessment of end points; subjects followed for a median of 4.1 years	6,083 participants with hypertension in the ages 65-84	antihypertensive treatment involving ACE inhibitors in older subjects, particularly men, appears to lead to better outcomes than treatment with diuretic agents, despite similar reductions of blood pressure.
JNC VII	Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT)[85]	2002	randomized, double-blind, active-controlled clinical trial; February 1994-March 2002	33,357 participants aged 55 years or older with hypertension and at least one other CHD risk factor	thiazide-type diuretics are superior to calcium-channel blockers and ACE inhibitors in preventing one or more major forms of CVD and are less expensive
JNC VI	Systolic Hypertension in Europe Trial (Syst-Eur)[86]	1997	randomized, double-blind, placebo-controlled clinical trial, 1989-1997, with a median of 2 years follow-up	4,695 participants with hypertension over the age of 60	antihypertensive treatment involving calcium antagonists of elderly patients with isolated systolic hypertension led to reductions in cardiovascular complications
JNV VI	Evaluation of Losartan in the Elderly Study (ELITE)[87]	1997	randomized, double-blind, active controlled clinical trial of losartan (angiotensin II receptor blocker) or captopril (ACE inhibitor)	722 ACE inhibitor naïve patients	in this study of elderly heart failure patients, treatment with losartan led to lower mortality than treatment with captopril. losartan also appeared to be better tolerated and fewer patients in this cohort discontinued use

JNC VI	Australia/New Zealand Heart Failure Research Collaborative Group trial of carvedilol[88]	1997	randomized, double-blind, placebo-controlled trial of carvedilol (beta blocker)	415 patients with chronic heart failure	carvedilol improved left ventricular valve function and size
JNC VI	US Carvedilol Heart Failure Study Group[89]	1996	randomized, double-blind placebo-controlled trial of carvedilol (beta blocker)	1,094 patients with chronic heart failure	carvedilol reduces the risk of death as well as the risk of hospitalization for cardiovascular causes in patients with heart failure who are receiving treatment with digoxin, diuretics, and an ACE inhibitor.
JNC V	Systolic Hypertension in the Elderly Program (SHEP)[90]	1991	randomized, double-blind, placebo-controlled trial of chlorthalidone (diuretic) as step 1 and atenolol (beta blocker) as step 2	4,736 participants over 60 years of age with isolated systolic hypertension	stepped-care drug treatment with low-dose chlorthalidone as step 1 medication reduced the incidence of total stroke by 36%, with 5-year absolute benefit of 30 events per 1000 participants. Major cardiovascular events were reduced, with 5-year absolute benefit of 55 events per 1000.
JNC V	Studies of Left Ventricular Dysfunction (SOLVD)[91]	1991	randomized, double-blind, placebo-controlled trial of enalapril (ACE inhibitor)	2,569 patients receiving conventional treatment for heart failure	The addition of enalapril to conventional therapy significantly reduced mortality and hospitalizations for heart failure in patients with chronic congestive heart failure and reduced ejection fractions.
JNC V	Comparison of enalapril with hydralazine-isosorbide dinitrate in treatment of chronic congestive heart failure[92]	1991	randomized, double-blind, active-controlled trial of enalapril (ACE inhibitor) versus hydralazine plus isosorbide dinitrate	804 men receiving digoxin and diuretic therapy for heart failure	vasodilator therapy should be included in the standard treatment for heart failure

JNC V	Swedish Trial in Old Patients Hypertension (STOP-Hypertension) [93]	1991	prospective, randomized, double-blind placebo-controlled trial of atenolol, hydrochlorothiazide plus amiloride, metoprolol, and pindolol (four arms)	1,627 patients with hypertension aged 70-84 years	antihypertensive treatment in hypertensive men and women aged 70-84 confers highly significant reductions in cardiovascular morbidity and mortality
JNC IV	Benefits and Potential Harm of Lowering High Blood Pressure[94]	1987	open label study of atenolol (beta blocker) alone or in combination with hydralazine, prazosin, or nifedipine (diuretics)	902 patients; recruited between 1972 and 1982, inclusive	lowering *diastolic* blood pressure in older patients with evidence of ischaemic heart disease increases their risk of dying from myocardial infarction [J-curve relation]
JNC IV	MRC Trial of Treatment of Mild Hypertension[95]	1985	randomized, single-blind, active- and placebo-controlled trial of bendrofluazide (diuretic) or propranolol (beta blockers)	17,354 men and women between 35-64 years	a comparison of the two drugs showed that the reduction in stroke rate on bendrofluazide was greater than that on propranolol; active treatment, however, made no difference to the overall rate of coronary events
JNC IV	Australian Therapeutic Trial in Mild Hypertension[96]	1980	randomized placebo-controlled study of chlorothiazide (diuretic) initially, followed by increasing dose or second-order therapy (methyldopa, propranolol, or pindolol), followed by third-order therapy if necessary (hydralazine or clonidine)	3,425 men and women of age 30-69 years with mild hypertension and free of clinical evidence of cardiovascular disease	the actively-treated group had a 2/3 reduction in deaths from cardiovascular disease, compared to the placebo group

JNC IV	Hypertension Detection and Follow-up Program (HDFP)[97]	1979	community-based randomized study of "stepped care" provided via special centers versus "referred care" provided via their usual sources of care	10,940 patients with high blood pressure aged 30-69 years	control of blood pressure was consistently better for patients in the stepped care group; thus the systemic effective management of hypertension has great potential for reducing mortality
JNC IV	Veterans Administration Cooperative Study Group on Antihypertensive Agents[98]	1970	randomized, double-blind, placebo-controlled trial of a combination therapy (hydrochlorothiazide + reserpine) or hydralazine hydrochloride	380 male hypertensive patients with diastolic blood pressures averaging 90 to 114 mmHg	antihypertensive treatment reduced morbidity and mortality in middle-aged men with sustained elevated diastolic blood pressure

Appendix III: Regression Analysis Results

SUMMARY OUTPUT

Regression Statistics	
Multiple R	0.7164122
R Square	0.5132465
Adjusted R Square	0.4758039
Standard Error	70.616815
Observations	15

Regression analysis for average number of patients per pivotal trial

Explanatory variables:
1. submission date

ANOVA

	df	*SS*	*MS*	*F*	*Significance F*
Regression	1	68355.96803	68355.96803	13.70756	0.002658
Residual	13	64827.54936	4986.734566		
Total	14	133183.5174			

	Coefficients	*Standard Error*	*t Stat*	*P-value*	*Lower 95%*	*Upper 95%*	*Lower 95.0%*	*Upper 95.0%*
Intercept	187.91092	40.31506107	4.661060111	0.000446	100.815529	275.006317	100.81553	275.00632
X Variable 1	0.0527473	0.014246888	3.702372341	0.002658	0.02196875	0.08352581	0.0219688	0.0835258

SUMMARY OUTPUT

Regression analysis for average number of patients per pivotal trial

Explanatory variables:
1. submission date
2. dummy variable for beta blocker
3. dummy variable for calcium channel
4. dummy variable for diuretic
5. dummy variable for ACE inhibitor (angiotensin II receptor antagonists as reference class)

Regression Statistics	
Multiple R	0.82946056
R Square	0.68800482
Adjusted R Square	0.51467417
Standard Error	67.9481951
Observations	15

ANOVA

	df	*SS*	*MS*	*F*	*Significance F*
Regression	5	91630.90248	18326.1805	3.96932	0.035249329
Residual	9	41552.61491	4616.957213		
Total	14	133183.5174			

	Coefficients	*Standard Error*	*t Stat*	*P-value*	*Lower 95%*	*Upper 95%*	*Lower 95.0%*	*Upper 95.0%*
Intercept	-1432.8558	659.4773951	-2.172714009	0.057857	-2924.69729	58.98573473	-2924.6973	58.9857347
X Variable 1	0.05122246	0.018597836	2.754215879	0.022322	0.009151228	0.093293685	0.00915123	0.09329369
X Variable 2	30.1034647	77.00324782	0.390937597	0.704937	-144.089984	204.2969129	-144.08998	204.296913
X Variable 3	-5.940024	69.30598446	-0.08570723	0.933576	-162.721053	150.8410049	-162.72105	150.841005
X Variable 4	-96.660014	54.57413307	-1.771169019	0.110303	-220.115279	26.79525206	-220.11528	26.7952521
X Variable 5	-65.238075	53.99784095	-1.208160813	0.257772	-187.389678	56.913527	-187.38968	56.913527

SUMMARY OUTPUT

Regression analysis for average number of patients per pivotal trial

Explanatory variables:
1. submission date
2. dummy variable for beta blockers plus diuretics
3. dummy variable for calcium channel blockers
4. dummy variable for ACE inhibitors (angiotensin II receptor antagonists as reference class)

Regression Statistics	
Multiple R	0.78292963
R Square	0.6129788
Adjusted R Square	0.45817032
Standard Error	71.7947384
Observations	15

ANOVA

	df	*SS*	*MS*	*F*	*Significance F*
Regression	4	81638.67273	20409.66818	3.959594	0.0352958
Residual	10	51544.84466	5154.484466		
Total	14	133183.5174			

	Coefficients	*Standard Error*	*t Stat*	*P-value*	*Lower 95%*	*Upper 95%*	*Lower 95.0%*	*Upper 95.0%*
Intercept	-1181.4536	673.0092537	-1.755479043	0.109704	-2681.0117	318.104419	-2681.0117	318.104419
X Variable 1	0.04412732	0.018978409	2.325132475	0.0424	0.00184078	0.08641385	0.00184078	0.08641385
X Variable 2	-58.471037	50.72251922	-1.152762869	0.275819	-171.487852	54.5457785	-171.48785	54.5457785
X Variable 3	-22.283682	72.28245106	-0.308286191	0.764191	-183.339018	138.771655	-183.33902	138.771655
X Variable 4	-75.455079	56.58078902	-1.333581237	0.21192	-201.524932	50.6147751	-201.52493	50.6147751

SUMMARY OUTPUT

Regression Statistics	
Multiple R	0.403761534
R Square	0.163023376
Adjusted R Square	0.079325714
Standard Error	447.1303636
Observations	12

Regression analysis for size of safety database per FDA pivotal trial (n=12)

Explanatory variables:
1. submission date

ANOVA

	df	*SS*	*MS*	*F*	*Significance F*
Regression	1	389408.0104	389408.0104	1.947765	0.19304158
Residual	10	1999255.621	199925.5621		
Total	11	2388663.631			

	Coefficients	*Standard Error*	*t Stat*	*P-value*	*Lower 95%*	*Upper 95%*	*Lower 95.0%*	*Upper 95.0%*
Intercept	476.7751589	326.3912021	1.460747581	0.17478	-250.469756	1204.02007	-250.469756	1204.02007
X Variable 1	0.151488617	0.108545475	1.395623513	0.193042	-0.09036577	0.39334301	-0.09036577	0.39334301

SUMMARY OUTPUT

Regression analysis for number of FDA pivotal trials per NDA

Explanatory variables:
1. submission date

Regression Statistics	
Multiple R	0.421631422
R Square	0.177773056
Adjusted R Square	0.11452483
Standard Error	2.139899903
Observations	15

ANOVA

	df	*SS*	*MS*	*F*	*Significance F*
Regression	1	12.87076928	12.87076928	2.810720021	0.117504204
Residual	13	59.52923072	4.579171594		
Total	14	72.4			

	Coefficients	*Standard Error*	*t Stat*	*P-value*	*Lower 95%*	*Upper 95%*	*Lower 95.0%*	*Upper 95.0%*
Intercept	7.026707728	1.221666472	5.751739849	6.69032E-05	4.387457779	9.6659577	4.38745778	9.66595768
X Variable 1	-0.000723793	0.000431723	-1.676520212	0.117504204	-0.001656474	0.0002089	-0.0016565	0.00020889

SUMMARY OUTPUT

Regression analysis for ratio of FDA pivotal trials to total number of clinical studies in NDA

Explanatory variables:
1. submission date

Regression Statistics	
Multiple R	0.25268597
R Square	0.063850199
Adjusted R Square	-0.008161324
Standard Error	0.068508945
Observations	15

ANOVA

	df	*SS*	*MS*	*F*	*Significance F*
Regression	1	0.004161547	0.004161547	0.886666	0.363552162
Residual	13	0.061015183	0.004693476		
Total	14	0.06517673			

	Coefficients	*Standard Error*	*t Stat*	*P-value*	*Lower 95%*	*Upper 95%*	*Lower 95.0%*	*Upper 95.0%*
Intercept	0.103627497	0.039111681	2.649528103	0.02003	0.019131848	0.18812315	0.019131848	0.188123146
X Variable 1	1.30149E-05	1.38216E-05	0.941629662	0.363552	-1.6845E-05	4.2875E-05	-1.6845E-05	4.28747E-05

SUMMARY OUTPUT

Regression analysis for average number of arms per pivotal trial

Explanatory variables:
1. submission date

Regression Statistics	
Multiple R	0.583242138
R Square	0.340171391
Adjusted R Square	0.289415345
Standard Error	0.867025707
Observations	15

ANOVA

	df	*SS*	*MS*	*F*	*Significance F*
Regression	1	5.038183085	5.038183085	6.70208601	0.022476827
Residual	13	9.772536492	0.751733576		
Total	14	14.81071958			

	Coefficients	*Standard Error*	*t Stat*	*P-value*	*Lower 95%*	*Upper 95%*	*Lower 95.0%*	*Upper 95.0%*
Intercept	3.330183894	0.495019292	6.727382036	1.41024E-05	2.260759733	4.39960806	2.26075973	4.39960806
X Variable 1	0.000452801	0.000174905	2.588838738	0.022476827	7.49416E-05	0.00083066	7.4942E-05	0.00083066

SUMMARY OUTPUT

Regression Statistics	
Multiple R	0.777853513
R Square	0.605056088
Adjusted R Square	0.447078523
Standard Error	0.764813934
Observations	15

Regression analysis for average number of arms per pivotal trial

Explanatory variables:
1. submission date
2. dummy variable for diuretics plus beta blockers
3. dummy variable for calcium channel blockers
4. dummy variable for ACE inhibitors, with angiotensin II receptor antagonists as the reference class

ANOVA

	df	*SS*	*MS*	*F*	*Significance F*
Regression	4	8.961316043	2.240329011	3.830013	0.038678824
Residual	10	5.849403534	0.584940353		
Total	14	14.81071958			

	Coefficients	*Standard Error*	*t Stat*	*P-value*	*Lower 95%*	*Upper 95%*	*Lower 95.0%*	*Upper 95.0%*
Intercept	2.273146267	0.714879664	3.179760707	0.009823	0.680295119	3.865997415	0.68029512	3.86599741
X Variable 1	0.000716552	0.000202173	3.544254309	0.005319	0.000266083	0.001167022	0.00026608	0.00116702
X Variable 2	-0.124336205	0.540336107	-0.230109007	0.822646	-1.32828007	1.079607663	-1.32828007	1.07960766
X Variable 3	1.083911404	0.770009432	1.407659905	0.189549	-0.63177652	2.799599327	-0.63177652	2.79959933
X Variable 4	1.358025693	0.602742997	2.253075853	0.047929	0.015030609	2.701020777	0.01503061	2.70102078

SUMMARY OUTPUT

Regression analysis for number of arms per pivotal trial

Explanatory variables:
1. submission date
2. dummy variable for beta blockers
3. dummy variable for calcium channel blockers
4. dummy variable for diuretics
5. dummy variable for ACE inhibitors (angiotensin II receptor antagonists are reference class)

Regression Statistics	
Multiple R	0.78024037
R Square	0.60877503
Adjusted R Square	0.39142782
Standard Error	0.80238003
Observations	15

ANOVA

	df	*SS*	*MS*	*F*	*Significance F*
Regression	5	9.016396223	1.803279245	2.800933	0.085240815
Residual	9	5.794323353	0.643813706		
Total	14	14.81071958			

	Coefficients	*Standard Error*	*t Stat*	*P-value*	*Lower 95%*	*Upper 95%*	*Lower 95.0%*	*Upper 95.0%*
Intercept	2.21927372	0.772277847	2.873672637	0.018366	0.472259858	3.96628758	0.47225986	3.966287578
X Variable 1	0.00073321	0.000219616	3.338597128	0.00868	0.000236404	0.00123002	0.0002364	0.001230017
X Variable 2	0.08362158	0.909308451	0.091961735	0.928743	-1.97337704	2.1406202	-1.973377	2.140620203
X Variable 3	1.12228352	0.818413757	1.37129112	0.203501	-0.72909702	2.97366406	-0.729097	2.973664056
X Variable 4	-0.2139974	0.644449706	-0.332062211	0.747445	-1.67184391	1.24384912	-1.6718439	1.24384912
X Variable 5	1.38201347	0.637644443	2.167373187	0.058363	-0.06043847	2.82446541	-0.0604385	2.824465411

SUMMARY OUTPUT

Regression Statistics	
Multiple R	0.5677869
R Square	0.32238197
Adjusted R Square	0.2702575
Standard Error	1.86785013
Observations	15

Regression analysis for number of drug-drug interaction studies

Explanatory variables:
1. submission date

ANOVA

	df	*SS*	*MS*	*F*	*Significance F*
Regression	1	21.57809978	21.57809978	6.18485	0.02725166
Residual	13	45.35523355	3.488864119		
Total	14	66.93333333			

	Coefficients	*Standard Error*	*t Stat*	*P-value*	*Lower 95%*	*Upper 95%*	*Lower 95.0%*	*Upper 95.0%*
Intercept	3.90122455	1.066429569	3.658211155	0.002892	1.597343535	6.2051056	1.597343535	6.20510556
X Variable 1	0.00093708	0.000376801	2.486935781	0.027252	0.000123051	0.0017511	0.000123051	0.00175111

SUMMARY OUTPUT

Regression Statistics	
Multiple R	0.019763567
R Square	0.000390599
Adjusted R Square	-0.08291018
Standard Error	0.055632818
Observations	14

Regression analysis for percentage of discontinued patients in FDA pivotal trials

Explanatory variables:
1. submission date

ANOVA

	df	*SS*	*MS*	*F*	*Significance F*
Regression	1	1.45125E-05	1.45125E-05	0.004689	0.94653422
Residual	12	0.037140125	0.00309501		
Total	13	0.037154638			

	Coefficients	*Standard Error*	*t Stat*	*P-value*	*Lower 95%*	*Upper 95%*	*Lower 95.0%*	*Upper 95.0%*
Intercept	0.126601013	0.03287739	3.850701384	0.002307	0.054967333	0.19823469	0.05496733	0.198234693
X Variable 1	-7.7855E-07	1.13697E-05	-0.068476377	0.946534	-2.5551E-05	2.3994E-05	-2.5551E-05	2.39938E-05

SUMMARY OUTPUT

Regression analysis for percentage discontinued patients in FDA pivotal trials, first two data points dropped

Explanatory variables:
1. submission date

Regression Statistics	
Multiple R	0.4438163
R Square	0.1969729
Adjusted R Square	0.1166702
Standard Error	0.0456603
Observations	12

ANOVA

	df	*SS*	*MS*	*F*	*Significance F*
Regression	1	0.005113925	0.005113925	2.45288	0.148378111
Residual	10	0.020848652	0.002084865		
Total	11	0.025962577			

	Coefficients	*Standard Error*	*t Stat*	*P-value*	*Lower 95%*	*Upper 95%*	*Lower 95.0%*	*Upper 95.0%*
Intercept	0.8125546	0.433031825	1.876431551	0.090051	-0.15230045	1.7774096	-0.1523005	1.77740961
X Variable 1	-1.93E-05	1.23256E-05	-1.566167358	0.148378	-4.6767E-05	8.159E-06	-4.677E-05	8.1592E-06

SUMMARY OUTPUT

Regression Statistics	
Multiple R	0.32573246
R Square	0.10610164
Adjusted R Square	-0.2911865
Standard Error	0.06074763
Observations	14

Regression analysis of percentage discontinued patients in FDA pivotal trials

Explanatory variables:
1. submission date
2. dummy variable for beta blockers and diuretics
3. dummy variable for calcium channel blockers
4. dummy variable for ACE inhibitors, with angiotensin II receptor antagonists as reference class

ANOVA

	df	*SS*	*MS*	*F*	*Significance F*
Regression	4	0.003942168	0.000985542	0.267065	0.891890623
Residual	9	0.03321247	0.003690274		
Total	13	0.037154638			

	Coefficients	*Standard Error*	*t Stat*	*P-value*	*Lower 95%*	*Upper 95%*	*Lower 95.0%*	*Upper 95.0%*
Intercept	-0.0885223	0.569493618	-0.15544042	0.879905	-1.376806393	1.19976174	-1.37680639	1.199761738
X Variable 1	5.633E-06	1.60593E-05	0.350763008	0.733836	-3.06957E-05	4.1962E-05	-3.0696E-05	4.19618E-05
X Variable 2	0.02971799	0.042917949	0.692437229	0.506134	-0.06736916	0.12680513	-0.06736916	0.126805132
X Variable 3	0.02520411	0.061161902	0.412088455	0.689917	-0.113153721	0.16356195	-0.11315372	0.163561949
X Variable 4	0.05068711	0.053790825	0.942300211	0.370643	-0.070996195	0.17237041	-0.07099619	0.172370407

SUMMARY OUTPUT

Regression analysis for percentage discontinued patients in FDA pivotal trials

Explanatory variables:
1. submission date
2. dummy variable representing first-in-class drugs

Regression Statistics	
Multiple R	0.142095395
R Square	0.020191101
Adjusted R Square	-0.15795597
Standard Error	0.05752821
Observations	14

ANOVA

	df	*SS*	*MS*	*F*	*Significance F*
Regression	2	0.000750193	0.000375097	0.11334	0.893876638
Residual	11	0.036404445	0.003309495		
Total	13	0.037154638			

	Coefficients	*Standard Error*	*t Stat*	*P-value*	*Lower 95%*	*Upper 95%*	*Lower 95.0%*	*Upper 95.0%*
Intercept	0.173089029	0.411690362	0.420434978	0.682264	-0.73303535	1.079213406	-0.7330353	1.079213406
X Variable 1	-1.3363E-06	1.18164E-05	-0.113091775	0.911995	-2.7344E-05	2.46714E-05	-2.734E-05	2.46714E-05
X Variable 2	-0.02828946	0.060001325	-0.471480528	0.646511	-0.16035148	0.103772569	-0.1603515	0.103772569

SUMMARY OUTPUT

Regression analysis for FDA approval time for each NDA

Explanatory variables:
1. submission date

Regression Statistics	
Multiple R	0.823648914
R Square	0.678397533
Adjusted R Square	0.653658882
Standard Error	162.2342113
Observations	15

ANOVA

	df	*SS*	*MS*	*F*	*Significance F*
Regression	1	721760.5223	721760.5223	27.42257548	0.000160534
Residual	13	342159.211	26319.93931		
Total	14	1063919.733			

	Coefficients	*Standard Error*	*t Stat*	*P-value*	*Lower 95%*	*Upper 95%*	*Lower 95.0%*	*Upper 95.0%*
Intercept	1065.043618	92.61933058	11.49915046	3.47886E-08	864.9517196	1265.13552	864.95172	1265.13552
X Variable 1	-0.17139906	0.032730627	-5.236656899	0.000160534	-0.24210928	-0.1006888	-0.2421093	-0.1006888

Appendix IV: Example of Inclusion/Exclusion Criteria for a Clinical Trial

Douglass et al. (1978) defined the following selection criteria for patients in a trial of chemotherapy for advanced colorectal cancer:[99]

(1) Patients must have histologically confirmed metastatic or locally recurrent carcinoma of the colon or rectum.
(2) Tumor must be beyond hope of surgical eradication.
(3) There must be tumor masses that can clearly be measured on physical examination or chest X-ray.
(4) No previous chemotherapy for their disease.
(5) An expected survival of at least 90 days and absence of severe malnutrition, nausea, and vomiting.
(6) Patients must have recovered from effects of major surgery.
(7) Patients must have white cell count >4000 per mm^3, platelet count >100,000 per mm^3, hemoglobin >10 g per 100 mL, and creatinine <1.5 mg per 100 mL.
(8) Patients must be informed of the nature of their disease and their written consent must be obtained before instituting therapy.

[1] DiMasi, J. A., Hansen, R. W., and Grabowski, H. G., "The Price of Invention: New Estimates of Drug Development Costs," *Journal of Health Economics*, vol. 22, no. 2 (March 2003), pp. 151-185.
[2] Congressional Budget Office, "Research and Development in the Pharmaceutical Industry," October 2006, p. 2.
[3] Source: Congressional Budget Office based on National Science Foundation table "Company and Other (Except Federal) Funds for Industrial R&D Performance, by Industry and by Size of Company: 1953-98," available at www.nsf.gov/statistics/iris/search_hist.cfm?indx=10; and Bronwyn H. Hall, Adam B. Jaffe, and Manuel Tratjenberg, The NBER Patent Citation Data File: Lessons, Insight, and Methodological Tools, Working Paper No. 8498 (Cambridge, Mass.: National Bureau of Economic Research, October 2001), taken from Congressional Budget Office, "Research and Development in the Pharmaceutical Industry," October 2006, p. 38.
[4] DiMasi, *et al*, pp. 167-168.
[5] Food and Drug Administration, *Innovation and Stagnation: Challenge and Opportunity on the Critical Path to New Medical Products* (March 2004), p. 8, as cited in CBO, October 2006, p. 23.
[6] DiMasi, *et al*, pp. 162-177.
[7] DiMasi, "New Drug Development in the United States from 1963 to 1999," as cited in CBO, October 2006, p. 23.
[8] Association of University Technology Managers, *AUTM U.S. Licensing Survey: FY 2004—Survey Summary* (Northbrook, Ill.: AUTM, 2005), p. 26, available at www.autm.net/events/File/FY04%20Licensing%20Survey/04AUTM-USLicSrvy-public.pdf
[9] Alper, A., *et al*, "Hypertension," *Encyclopedia of the Life Sciences*, John Wiley & Sons, 2001, p. 1 (http://www.els.net).
[10] The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure," US Department of Health and Human Services, NIH Publication No. 04-5230, August 2004, p. 1.
[11] *Ibid.* p. 2.
[12] Chobanian, A., *et al*, "Seventh Report of the Joint National Committee on the Prevention, Detection, Evaluation, and Treatment of High Blood Pressure," *Hypertension*, **42**, (2003): p. 1207.
[13] Cutler, D., *et al*, "The Value of Antihypertensive Drugs: A Perspective on Medical Innovation," *Health Affairs*, **26**, No. 1, (2007): pp. 97-110.
[14] "Arterial Hypertension," Section 199 of Beers, M., *et al*, eds., *The Merck Manual of Diagnosis and Therapy, 17th Edition*, Merck & Co., 1999, accessed online at http://online.statref.com/document.aspx?fxid=21&docid=578 on March 3, 2006 at 11:51am.
[15] Hamilton, B.P. and Blaustein, M.P., "Molecular Mechanisms Linking Sodium to Hypertension: Report of a Symposium," *J. Invest. Med.* **54, (**2006): pp. 86-94.
[16] Gress, T.W., *et al*, "Hypertension and Antihypertensive Therapy as Risk Factors for Type 2 Diabetes Mellitus," *NEJM* **342, (**2000): pp. 905-912.
[17] Schwartz, G., *et al*, "Hypertension," article in ACP Medicine (2006), accessed online at http://online.statref.com/Document/Document.aspx?DocId=154&FxId=48&Scroll=1&Index=0&SessionId=8221E4JPKJDOFIIV on 3/1/2006 at 11:58am.
[18] Beers, M., *et al*, eds.
[19] Moser, M., "Evolution of the Treatment of Hypertension from the 1940s to JNC V," *Am. Journal of Hypertension*, **10**, (1997), p. 2S.
[20] *Ibid.* p. 3S.
[21] *Ibid.* p. 2S.
[22] Cutler, D., *Your Money or Your Life*, Oxford University Press, New York, NY, 2004, p. 50.
[23] US Public Health Service, *High Blood Pressure* (Washington, DC: Government Printing Office, 1948).
[24] Moser, (1997): p. 4S.
[25] *Ibid.* p. 3S.
[26] The Sixth Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure, *Arch Intern Med.* **157, (**1997): pp. 2413-2446.
[27] Lloyd-Jones, D.M., *et al*, "Differential Control of Systolic and Diastolic Blood Pressure: Factors Associated with Lack of Blood Pressure Control in the Community," *Hypertension*, **36**, (2000): pp. 597.
[28] Fagan, T., "Evolution of the Joint National Committee Reports, 1988-1997," *Arch. Intern. Med.* **157**, (1997): p. 2401.

[29] Black, H., "The Paradigm Has Shifted, to Systolic Blood Pressure," *Hypertension* **34,** (1999): 386-387.
[30] The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure," US Department of Health and Human Services, NIH Publication No. 04-5230, August 2004, p. 14.
[31] Lloyd-Jones, *et al,* p. 594.
[32] Benowitz, N., "Antihypertensive Agents," article in *STAT!Ref Online Electronic Medical Library,* Katzung, B., editor, 2004, McGraw-Hill.
[33] Alper, *et al,* p. 7.
[34] Moser, M., (1997): p. 6S.
[35] Moser, M., "Prevention of Disease Progression, Left Ventricular Hypertrophy and Congestive Heart Failure in Hypertension Treatment Trials," *J. Am. Coll. Cardiology,* **27,** No. 5, (1996): pp. 1214-1218.
[36] Fagan, T., p. 2401.
[37] Pitt, B., *et al,* "Randomized trial of losartan versus captopril in patients over 65 with heart failure (Evaluation of Losartan in the Elderly Study, ELITE)," *The Lancet,* **349,** (1997): pp. 747-752.
[38] Packer, M., "The Effect of Carvedilol on Morbidity and Mortality in Patients with Chronic Heart Failure," *NEJM,* **334,** No. 21, (1996): pp.1349-1355.
[39] Cohn, J., *et al,* "Effect of the Calcium Antagonist Felodipine as Supplementary Vasodilator Therapy in Patients With Chronic Heart Failure Treated With Enalapril," *Circulation,* **96,** (1997): pp. 856-863.
[40] *Ibid.* p. 2401.
[41] *Ibid.* p. 2401.
[42] *Ibid.* p. 2402.
[43] *Ibid.* p. 2402.
[44] Jones, D., *et al,* "Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure and Evidence from New Hypertension Trials," *Hypertension,* **43,** (2004): p. 1.
[45] "The Sixth Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure." *Arch Intern Med,* **157,** (1997): pp. 2413–46.
[46] "The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure." *JAMA,* **289,** (2003): pp. 2560–71.
[47] Jones, D., *et al,* p. 2.
[48] *Complete Drug Reference,* Consumer Reports Books, 1995 Edition, Yonkers, NY, p. 741.
[49] http://www.nlm.nih.gov/medlineplus/druginfo/uspdi/500431.html, viewed on 11/14/2006 at 10:30pm.
[50] *Ibid.* p. 410.
[51] *Ibid.* pp. 471-472.
[52] *Ibid.* pp. 248-249.
[53] ACP Medicine online, via STAT-Ref, http://online.statref.com/Document/Document.aspx?DocId=164&FxId=48&Scroll=1&Index=0&SessionId=80EEC1PZVHBRNGOM viewed on 11/7/06 at 1:30pm via MIT libraries (Vera)
[54] Messerli, F., "ALLHAT, or the Soft Science of the Secondary End Point," *Annals of Internal Medicine,* **139,** (2003): pp. 777-780.
[55] Jones, D., *et al,* p. 2.
[56] Beers, M., *et al,* eds., *The Merck Manual of Diagnosis and Therapy, 2nd Home Edition,* Merck & Co. 2003, p. 131.
[57] Taylor, A., Wright, J., "Should Ethnicity Serve as the Basis for Clinical Trial Design?" *Circulation,* **112,** (2005): pp. 3654-3666.
[58] *Ibid.* p 3655.
[59] Pocock, S.J., *Clinical Trials: A Practical Approach,* John Wiley & Sons, New York, NY, 1983, p. 2.
[60] Berndt, E. R., discussion with J. S. MacNeil, April 24, 2007.
[61] Pocock, S.J., p. 3.
[62] This figure is reproduced from Berndt, Gottschalk, and Strobeck [2005], which in turn is constructed in part from data cited by Mathiew, M.P. ed. (2003/2004), "Development Pipeline Attrition" and "Attrition Rates (Probability of Success) Used by 29 Companies for Planning Purposes in 1998," PAREXEL 2002/2003 Pharmaceutical R&D Statistical Sourcebook, Waltham, MA, p. 184, based on studies at the Tufts Center for the Study of Drug Development, Hambrecht & Quist estimates.

[63] Berndt, E. R., Gottschalk, A., Strobeck, M. W., "Opportunities for Improving the Drug Development Process: Results from a Survey of Industry and the FDA," National Bureau of Economic Research, Working Paper 11425, June 2005.
[64] *Ibid*, p. 9.
[65] Pocock, S.J., p. 7.
[66] Bernstein, Ilisa, "NDA Review Data Project Training Session," slide presentation to MIT-FDA team, January 13, 2006.
[67] http://www.fda.gov/cder/drug/drugInteractions/default.htm#background, viewed on 11/13/2006 at 10:30pm
[68] Mosby's Drug Consult, 16th Edition, 2006. Accessed: 10/10/2006 9:27:37 PM PST (GMT -08:00). http://online.statref.com/document.aspx?fxid=26&docid=3560
[69] http://sec.edgar-online.com/1995/05/15/00/0000062391-95-000005/Section8.asp, viewed on 11/14/2006 at 6:05pm.
[70] *Ibid.*
[71] *Guidance for Industry: Drug Metabolism/Drug Interaction Studies in the Drug Development Process: Studies In Vitro*, FDA Guidance, April 1997, p. 2.
[72] *Guidance for Industry: In vivo Drug Metabolism/Drug Interaction Studies—Study Design, Data Analysis, and Recommendations for Dosing and Labeling*, FDA Guidance, November 1999, p. 3.
[73] Berndt, E.R., *et al*, "Industry Funding of the FDA: Effects of PDUFA on Approval Times and Withdrawal Rates," *Nature Reviews Drug Discovery*, **4**, (2005): pp. 545-554.
[74] Carpenter, D., Chernew, M., Smith, D. G., Fendrick, A. M., "Approval Times for New Drugs: Does the Source of Funding for FDA Staff Matter?" *Health Affairs*, 10.1377/hlthaff.w3.618, posting date December 17, 2003.
[75] Black, H., "The Paradigm Has Shifted, to Systolic Blood Pressure," *Hypertension*, **34**, (1999): pp. 386-387.
[76] *Ibid.* pp. 386-387.
[77] International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use, Draft ICH Consensus Principle, "Principles for Clinical Evaluation of New Antihypertensive Drugs," March 2000, pp. 1-2.
[78] DiMasi, J. A., Grawbowski, H. G., and Vernon, J., "R&D Costs and Returns by Therapeutic Category," *Drug Information Journal*, **38**, No. 3, (2004): pp. 211-223.
[79] The 1984 Report of the Joint National Committee on Detection, Evaluation, and Treatment of High Blood Pressure, Arch Intern Med, 144, (1984), pp. 1047.
[80] The 1988 Report of the Joint National Committee on Detection, Evaluation, and Treatment of High Blood Pressure, Arch Intern Med, 148, (1988), pp. 1024.
[81] The Fifth Report of the Joint National Committee on Detection, Evaluation, and Treatment of High Blood Pressure (JNC V), Arch Intern Med, 154, (1993), pp. 161.
[82] The Sixth Report of the Joint National Committee on Detection, Evaluation, and Treatment of High Blood Pressure, Arch Intern Med, 157, (1997), pp. 2417.
[83] The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure," US Department of Health and Human Services, NIH Publication No. 04-5230, August 2004, p. 12.
[84] Wing et. al., "A Comparison of Outcomes with Angiotensis-Converting-Enzyme Inhibitors and Diuretics for Hypertension in the Elderly," *NEJM*, **348**, No. 7 (2003), pp. 583-592.
[85] "Major Outcomes in High-Risk Hypertensive Patients Randomized to Angiotensin-Converting Enzyme Inhibitor or Calcium Channel Blocker vs Diuretic: The Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT)," *JAMA*, **288**, No. 23 (2002), pp. 2981-2997.
[86] Staessen, J., et. al., "Randomized double blind comparison of placebo and active treatment for older patients with isolated systolic hypertension," *The Lancet*, **350**, (1997), pp. 757-764.
[87] Pitt, B. et. al., "Randomised trial of losartan versus captopril in patients over 65 with heart failure (Evaluation of Losartan in the Elderly Study, ELITE)," *The Lancet*, **349**, (1997), pp. 747-752.
[88] MacMahon, S., et. al., "Randomised placebo-controlled trial of carvedilol in patients with congestive heart failure due to ischaemic heart disease," *The Lancet*, **349**, (1997), pp. 375-380.
[89] Packer, M., et. al., "The Effect of Carvedilol on Morbidity and Mortality in Patients with Chronic Heart Failure," *NEJM*, **334**, No. 21, (1996), pp. 1349-1355.
[90] "Prevention of stroke by antihypertensive drug treatment in older persons with isolated systolic hypertension. Final results of the Systolic Hypertension in the Elderly Program (SHEP)," *JAMA*, **265**, No. 24, (1991), pp. 3255-3264.

[91] "Effect of enalapril on survival in patients with reduced left ventricular ejection fractions and congestive heart failure," *NEJM*, **325**, No. 5, (1991), pp. 293-302.
[92] Cohn, J., et. al., "A comparison of enalapril with hydralazine-isosorbide dinitrate in the treatment of chronic congestive heart failure," *NEJM*, **325**, No. 5, (1991), pp. 303-310.
[93] Dahlof, B., et. al., "Morbidity and mortality in the Swedish trial in Old Patients with Hypertension (STOP-Hypertension)," *The Lancet*, **338**, No. 8778, (1991), pp. 1281-1285.
[94] Cruickshank, J. et al., "Benefits and Potential Harm of Lowering High Blood Pressure," *The Lancet*, **1**, (1987), pp. 581-583.
[95] Medical Research Council Working Party, "MRC trial of treatment of mild hypertension: principal results," *British Medical Journal*, **291**, (1985), pp. 97-104.
[96] "The Australian Therapeutic Trial in Mild Hypertension," *The Lancet*, **1**, (1980), pp. 1261-1267.
[97] Hypertension Detection and Follow-up Program Cooperative Group, "Five-year Findings of the Hypertension Detection and Follow-up Program," *JAMA*, **242**, (1979), pp. 2562-2571.
[98] Veterans Administration Cooperate Study Group on Antihypertensive Agents, "Effects of Treatment on Morbidity in Hypertension," *JAMA*, **213**, (1970), pp. 1143-1152.
[99] Pocock, S. J., *Clinical Trials: A Practical Approach*, John Wiley & Sons, New York, NY, 1983, p. 37.