Three Essays on the Pharmaceutical Industry

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Abstract

Three Essays on the Pharmaceutical Industry

Ariel Y. Fishman

Three essays discuss management theory and the pharmaceutical industry.

In the first essay: Managers cite value creation as a primary motivation for conducting acquisitions, yet empiricists have found that actual mergers are, on average, associated with a failure to create value for acquiring firms. Acquisition decisions, however, are endogenous to the expectations managers have about their eventual performance; a manager expecting to create value from an acquisition opportunity should be more likely to decide to acquire. This logic implies that managers with less accurate estimations of eventual performance would be more likely to make value-destroying merger decisions. I argue that, without the threat of market discipline, managers are less likely to make accurate calculations about expected value, and are consequently less likely to base merger decisions on such calculations. I support this argument by showing that undisciplined managers are more inclined to merge when others are also merging (via imitation), rather than simply in their own self-interest. I test this hypothesis by examining merger decisions among major pharmaceutical firms from 1987 to 2004.

In the second and third essays: Over the past 15 years, academic medical centers have ceased to be the primary locus of industry-sponsored clinical trial activity. Instead, clinical trials have increasingly been conducted in private
practices and for-profit, dedicated study sites. This paper examines the underlying causes of this startling evolution. On the demand side, the greater availability of non-academic investigators has enabled pharmaceutical firms to better match physicians' skills with specific projects. On the supply side, the paper argues that the growth of managed care health insurance has contributed to a rise in the number of non-academic physicians performing clinical research. In the second essay, coauthored with Pierre Azoulay, we find evidence consistent with these claims using a unique data set containing information about 85,919 site contracts for 7,735 clinical trials between 1991 and 2003. The third essay engages in a qualitative analysis of the same phenomenon, drawing on data generated by 70 interviews of two separate groups of physicians in 1999 and 2007.
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Preface

Fulfillment of the dissertation requirements presents doctoral students with two options of format: completion of a longer monograph on a single subject, or the completion of three related papers. The former approach takes advantage of economies of scale in data collection efforts and is more traditional in many disciplines. The latter approach, which I have selected, asks that the author prepare three essays worthy of submission to scholarly journals.

All three papers concern fundamental changes in the pharmaceutical industry over the past several decades. The first paper examines merger activity among large pharmaceutical firms, and asserts that not only can certain benefits to prospective mergers be identified ex-ante, but that the propensity of firms to engage in such mergers reflects characteristics of their corporate governance. The second (co-authored with Pierre Azoulay) and third papers describe a singular phenomenon through quantitative and qualitative lenses, respectively. That phenomenon has been the growth of clinical trial activity and the role of health insurance in its growth. In tandem, these papers hold that as managed care has gained prevalence in the U.S. economy, private physicians have increased their propensity to participate in clinical trial activity as part of the pharmaceutical industry.
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Many, many other friends and family helped me in countless ways; I cannot name them for fear of leaving too many off of the list, but they should know that their assistance is eternally appreciated. Most importantly, however, I thank Elana and my children, Atara and Lilah, for motivating me with their unconditional love and support, and my mother and father, whose desire to see me reach the finish line never went unnoticed.
I. Why Do They Buy?
Assessing the Relationship Between Corporate Governance and the Basis of Acquisition Decisions

Abstract

Although managers cite value creation as a primary motivation for conducting acquisitions, empiricists have found that actual mergers are, on average, associated with a failure to create value for acquiring firms. An acquisition decision, however, is endogenous to the expectations managers have about its eventual performance; a manager expecting to create value from an acquisition opportunity should consequently be more likely to decide to acquire. This logic implies that managers with less accurate estimations of eventual performance would be more likely to make value-destroying merger decisions. I argue that, without the threat of market discipline, managers are less likely to make accurate calculations about expected value, and are consequently less likely to base merger decisions on such calculations. I support this argument by showing that non-disciplined managers are more inclined to merge in times when others are also merging (via imitation), rather than simply in their firms’ self-interest. I test this hypothesis by examining merger decisions among major pharmaceutical firms from 1987 to 2004.
Earlier this decade [Pfizer CEO Hank McKinnell] pulled off two of the largest mergers in Big Pharma history... You can't begin to judge him until you understand what is known at Pfizer as “the cliff.” Go back to the mid-1990s, ... a confidential memo laid out a disquieting vision of what could happen sometime after the millennium. Key patents were due to expire.... For everyone privy to the report, including McKinnell, then a VP, a single page stood out. On it was a graphic that forecast a whopping 33% drop in Pfizer’s revenues over a three- to four-year period starting around 2003. “We called it the cliff,” says McKinnell. “Everything I’ve done has been to manage that challenge, and I think we’ve done a pretty good job.” (Simons, 2006).

1 Introduction

Mergers\(^1\) are one of the most substantial changes organizations can undergo, radically transforming the identities, finances, and operating structures of the firms involved. Managers cite many motivations for acquiring other firms, mostly under the rubric of value creation, whereby combining two firms yields a net benefit compared to keeping them as separate entities (often termed synergy; see Larsson & Finkelstein, 1999). Theorists have suggested numerous mechanisms through which mergers should create value, such as increased scale or scope economies, increased market power, or reductions of redundant costs. Empiricists,

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\(^1\) In the present paper, as is common in empirical research in this subject area, the terms merger and acquisition are used mostly interchangeably.
however, have found that actual mergers are, on average, associated with a failure to create any value for acquiring firms (Jensen & Ruback, 1983; Ravencraft & Scherer, 1987). Ensuing scholarship has consequently considered, among other possibilities, non-financial motivations for acquisition behavior ranging from the availability of private benefits for opportunistic managers (Avery, Chevalier, & Schaefer, 1998; Morck, Shleifer, & Vishny, 1990) to social pressures from sources such as executives at peer firms or investment bankers (Haunschild, 1993; Hayward, 2003).

Unobserved differences may also exist between merging and non-merging firms, raising the possibility that managers of value-destroying mergers are actually choosing the lesser of two evils, with merging simply yielding a smaller level of value destruction than not merging. Consider the case of Pfizer in this chapter's opening quote: While CEO Hank McKinnell had been criticized for going on an acquisition binge that adversely affected Pfizer's stock price (destroying value for shareholders), McKinnell\(^2\) defended his acquisition decisions as a means to attenuate more adverse outcomes associated with the forecasted revenue shortfall. In short, mergers are endogenous in nature: Managers will self-select whether or not to merge depending on the outcomes they expect. The population of merged firms consequently consists only of firms whose managers selected merging as a strategic choice. Under this logic, managers will merge

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\(^2\) McKinnell has a Ph.D. in Business from Stanford; Simons (2006) suggests that his decisions to acquire Pharmacia and Warner-Lambert were done with financial concerns holding primacy.
when they calculate that doing so creates more (or destroys less) value for their organizations than not merging.

Beyond the notion that endogeneity may account for the appearance of a lack of value creation, one common explanation for the existence of non-value creating acquisitions is that some managers do not choose the strategic option associated with a greater level of value creation for their firms. Some scholarship has considered why managers would do so. According to agency theory, for example, managers might select a strategic option benefiting them personally over the best interests of the firm if those managers are not affected by the threat of market discipline or some other incentive.

Less clear, however, is whether agency theory predicts that managers in such situations would be inclined to conduct more acquisitions or fewer. Some agency theorists have proposed that "empire building" would occur, in which non-disciplined managers conduct acquisitions to increase their personal status, wealth, or power (Baumol, 1959; Jensen, 1986). Others propose that fewer acquisitions would occur, following the "quiet life" model, in which non-disciplined managers avoid acquisitions or other opportunities to improve operating performance because they are effort averse (Bertrand & Mullainathan, 2003; Hicks, 1935). Notably, while it is possible to speculate on situations in which one or the other model would apply, both approaches have a common underlying assumption: Managers who deviate from the best interests of their firms, do so out of self-interest. Heterogeneity in performance, in this view, is causally linked to heterogeneity in the degree to which managers are insulated
from mechanisms (such as market discipline) that would otherwise curtail opportunism. This insulation, in turn, fosters a set of circumstances in which managers would be inclined to make relative value-destroying strategic decisions (Bertrand & Mullainathan, 1999, 2003; Core, Guay, & Rusticus, 2006; Gompers, Ishii, & Metrick, 2003).

Sociological research, on the other hand, has emphasized that managers operate in ambiguous environments, and that calculations associated with value creation opportunities are estimated with some uncertainty (March & Olsen, 1976). When such uncertainty is high, managers will look to their peers to determine the best courses of action to take (DiMaggio & Powell, 1983), either to maintain an image of rational behavior (Meyer & Rowan, 1977) or to avoid the risk that competitors might gain an advantage in taking that particular action (Abrahamson, 1991; Mansfield, 1961). Scholars have shown that this process of imitation occurs in strategic decisions ranging from market entry (Haveman, 1993), to selection of organizational form (Fligstein, 1985), to adoption of management practices in general (Abrahamson, 1991). Some have argued, however, that while this line of research has clearly established that social influence can drive strategic decisions, the question of the circumstances under which such imitation will take place remains less clear (Schneiberg & Clemens, 2006). Research under the auspices of herding behavior, for example, tends not to acknowledge heterogeneity in the tendency to follow a herd (Granovetter, 1978).

In the present chapter, I argue that corporate governance practices determine firms' tendencies to imitate their peers' actions. When market
discipline is high, market participants can replace ineffective managers by threatening a takeover (Manne, 1965). Certain corporate governance practices, however, can insulate managers from market discipline: They will either protect ineffective managers or enable managers to become effort averse. This insulation thus translates into a reduction in the accuracy and certainty with which managers will calculate the expected outcomes associated with strategic choices. Whereas agency theory predicts that non-disciplined managers will pursue their personal self-interests (without necessarily identifying the specific self-interest), I argue that non-disciplined managers will tend to imitate the actions of their peers. Managers who are uncertain as to whether merging would create value will choose to merge if others in their industry are doing so, and managers who are able to calculate value accurately will ignore others' decisions as a basis for their own behavior.

The remainder of this chapter proceeds as follows. First, I describe an empirical context where value creation opportunities can be calculated: the extent to which major pharmaceutical firms can use acquisitions to lessen the adverse impact of revenue shocks associated with patent expirations. I examine a population of 62 major pharmaceutical firms from 1987 to 2004 and evaluate the extent to which value creation opportunities drive the 26 mergers that occur among these firms in this time period. I follow this discussion by considering how corporate governance affects the propensity for firms to make acquisition decisions based on value creation opportunities, and consider the conditions under which other recent mergers in the industry might influence the acquisition
decision. I then present and interpret empirical findings to support these arguments, and conclude with a discussion of scholarly and practical implications.

2 Theory & Hypotheses

2.1 Determinants of acquisition decisions

Both theoretical and empirical scholarship has demonstrated that volatility in cash flows can affect firm operations, particularly with regard to investments in new product development (Froot, Scharfstein, & Stein, 1993; Minton & Schrand, 1999). Organizations depend on revenues generated by their current products to fund an internal capital market (Stein, 1997), providing a “source of funds for innovation that would not be approved in the face of scarcity” (Cyert & March, 1963: p. 278). The more managers can stabilize cash flows and efficiently utilize firm-specific assets, the greater an organization’s ability to rely on those resources to generate new innovations. Doing so is no easy task for managers: Buffer cash levels that are too high attract hostile takeovers and leveraged buyouts (Jensen, 1986; Manne, 1965), while cash levels that are too low increase the risk of cash shortfalls that cause organizations to forfeit investments in research and development (Minton & Schrand, 1999). Although firms could ostensibly borrow from external capital markets to cover cash shortfalls, the costs of borrowing are particularly high for firms in financial distress: External funding sources view firms’ internal investment opportunities as riskier than firms themselves do because of information asymmetries (Myers &
Majluf, 1984; Stein, 1997), and the volatility in the cash flow itself suggests to lenders that a firm may not have sufficient resources to make later debt payments (Froot et al., 1993).

Underutilization of firm-specific assets can also adversely affect firm performance. Building a manufacturing plant requires significant investment from a firm; excess or underused capacity reduces the financial return to that investment. A sales force dedicated to selling a patented product becomes unutilized once the patent expires. Underutilized assets not only represent wasted capacity but also increase the likelihood that market discipline will punish the managers of a firm squandering capital on those underutilized assets (Morck, Shleifer, & Vishny, 1988).

Mergers and acquisitions represent an important means for firms to stabilize the volatility in their cash flows and increase the efficient utilization of their assets. A firm can stabilize its cash flows particularly well if it merges with a partner whose cash flows have counterbalancing levels of volatility. That is to say, if one firm’s cash flows are anticipated to be high in year $t$ and low in year $t + 1$ while a prospective merger partner’s are low in year $t$ and high in year $t + 1$, the two firms can merge to increase the stability of their respective revenue streams (see Figure 1). For purposes of the present chapter, a pair of firms with counterbalanced cash flows is defined as having a high degree of fit.

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Insert Figure 1 about here
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Fit can also be considered conceptually in terms of a firm's non-financial assets, which may be more efficiently utilized if a firm merges with a partner whose assets complement its own in some way. For example, if one pharmaceutical firm's sales force has expertise selling a heart drug whose patent is expiring (i.e., a sales force without a product), while a second firm has a new heart drug being sold by an inadequately sized sales force without experience in heart medications (i.e., a product without a sales force), such firms can combine in order to maximize the utilization of their respective assets (i.e., the product and the sales force) more efficiently. While the first firm could simply downsize its sales force, or the second firm could divest rights to the patent for the new product, merging instead creates value for both firms. The first firm can extend the utilization of its sales force, and the second firm can accelerate sales of their product. Without merging, firms would have to obtain resources for utilizing their assets in an open market, where transaction costs (Williamson, 1975) could exceed the cost of merging.

One might argue that firms could instead use alliances or joint-ventures to utilize complementary assets. Villalonga and McGahan (2005), however, demonstrate that a firm's choice of an acquisition over an alliance or joint venture is particularly likely (1) when technological and marketing resources are involved, increasing the risk that a non-acquired partner misappropriates the knowledge it can now access, and (2) when the prospective relationship is horizontal rather than vertical, and the need to protect proprietary knowledge is highest. For firms in the same industry, merging affords firms the highest level of
mutual protection of intellectual property and the greatest ability to facilitate tacit knowledge sharing between the partner firms (Oxley & Sampson, 2004).

Properties of the pharmaceutical industry also make this line of reasoning particularly resonant with regard to cash flow stability. Because pharmaceutical firms are heavily dependent on patent-protected monopolies for revenue, cash flow shocks can be loosely anticipated more than a decade in advance by examining the timing of patent expirations. Every patent expiration can represent a substantial shock to a firm, because once a product's patent expires, that product can legally be manufactured by a competitor and sold at a price near marginal cost rather than a price determined by a firm's monopoly status. The introduction of unbranded "generic" versions of the same chemical compound commoditizes the market for that product, and drastically reduces the revenues once generated by the monopoly. For example, upon expirations of their respective patents, sales of Paxil dropped from $2.3 billion in 2002 to $171 million in 2004, Prozac dropped from $2.6 billion in 2000 to $392 million in 2002, Cipro dropped from $1 billion in 2002 to less than $200 million by 2004, and Prilosec dropped from nearly $4 billion in 2001 to $260 million by 2004. Many such patent monopolies generate a major proportion of their respective firms' annual revenues: Prozac, for example, represented 30% of Lilly's revenues in the years prior to its patent expiration. If a firm were to acquire another firm whose patents expire in different years from its own, that acquisition can reduce the impact of the revenue shocks for both firms and enable them to transition labor and capital resources from expiring products to newly developed ones.
Empirically, assessing how the degree of fit between a potential acquiror and target affects merger propensity requires an examination of all possible acquiror-target pairings in a population. While the logical underpinnings of why firms merge emphasizes that combining two firms can generate a net benefit compared to keeping them as separate entities, much of the empirical research on determinants of merger decisions is limited to examining how attributes of individual firms affect merger propensity. Moreover, studies of merger consequences attribute merger outcomes to traits endemic to the dyad of firms rather than to traits of individual acquirors (Barney, 1988; Chatterjee, 1986, 1992). The construct of fit utilized in the present chapter is calculated as a dyadic trait that varies for every possible pairing of acquirors and targets.

The importance of examining dyadic traits as merger determinants can be seen via analogy: Consider the notion of research analyzing marriage that only considered how traits of one person determined marriage likelihood. To increase external validity, a model should examine, in combination, (1) traits of the focal individual, (2) traits of prospective partners, and (3) attributes that are a function of the dyad examined as a unit. Since most dyads in a given population do not actually merge (or marry), it may appear difficult to measure traits commonly analyzed as determinants of post-merger performance, such as the size of acquisition premiums or the success of integration efforts. However, for a few types of traits—such as the existence of complementary resources, financial status, or membership in a network—calculation of dyadic traits is not only possible, but likely replicates the same decision-making process made by
managers in their own determinations of whether or not to acquire another firm. Indeed, some recent scholarship (Rhodes-Kropf, Robinson, & Viswanathan, forthcoming; Wang & Zajac, 2004, 2005) has trended toward the use of dyads rather than individual firms as the unit of analysis in examining merger propensity. This methodology has also been used in other contexts that involve examining propensities associated with dyadic situations, ranging from alliance formation (Gulati, 1995) to war between nations (King & Zeng, 2001).

The value creation opportunity available to merging firms, therefore, can be examined by comparing the schedule of patent expirations for two firms as separate entities to the schedule generated when those same two firms are treated as a potentially combined entity\(^3\). The relative stability of patent expirations over time can be calculated for each prospective acquiror, target, and pair of firms. The greater the stability of the combined firms' patent expiration schedule compared to the expiration schedule of the individual firms separately, the greater the fit, and the greater the value creation opportunity that merging presents\(^4\).

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\(^3\) The measurement of patent expiration schedules, of course, represents only a crude proxy of shocks to future revenues. The model would make the same prediction were future revenue data available; however, future patent expiration information is known with greater accuracy than future cash flow information.

\(^4\) Due to the law of large numbers, the average combination of firms will generally exhibit greater revenue stability than the individual firms. Because the shock of each patent expiration is spread across a larger denominator of total revenues, the effect of each expiration will generally less adverse. In the case of the opening quote in this paper, for example, Pfizer's acquisitions of Pharmacia and Warner-Lambert caused what would have been a 30% revenue shortfall to drop to a smaller value purely by spreading the impact of revenue shortfalls across a larger pool of resources. Even so, the greater the value creation opportunity, the more likely firms will merge.
Hypothesis 1: The propensity for a pair of firms to merge will increase as the fit between their patent expiration schedules increases.

Just as the fit in patent expiration schedules drives merger behavior, so can fit in firms’ R&D pipelines. Firms with full R&D pipelines will have drugs in numerous stages of development. Different personnel skills are involved in early-stage product development, which involves laboratory testing and small-scale clinical trials, versus late stage development, which requires management of large-scale clinical trials and frequent interaction with regulatory agencies. Gaps in the research pipeline, therefore, would leave specialized personnel underutilized and increases potential future revenue instability. A firm with a dearth of early-stage drugs but a plethora of late stage drugs would thus benefit from merging with a firm that has many early-stage products but fewer late stage drugs.

This logic is supported by rhetoric in the mainstream business press and anecdotal evidence supporting fit’s use as a basis for organizational decision-making. Paul Hastings, the CEO of Canadian drug manufacturer QLT Inc., was fired because of his inability to use his acquisition of Colorado-based Atrix Laboratories to fill gaps in the firm’s research pipeline (Zehr, 2005). A Wall Street Journal writer lamented the way mergers were used to “shore up weaknesses such as a lack of sufficient drugs in the pipeline to replace current drugs that are going off patent,” without firms’ addressing why product development pipelines have gaps in the first place (McGough & Deogun, 1999). Pfizer’s acquisition of Vicuron, a small biotech company, has been described as
providing it with “speedy access to drugs that complement its lineup” of products in the pipeline (Hopkins, 2005).

An alternative argument might suggest that organizations can acquire or divest individual products to stabilize their schedule of patent expirations or to fill their development pipelines. However, while firms may undertake such actions (and some anecdotal evidence says they do), the strategic choice to acquire a firm versus an individual product depends on several factors. Individual products under development bear a substantial degree of risk because they do not represent guaranteed future revenue streams. Only about 23% of Phase I, 33% of Phase II, and 78% of Phase III drugs will ever be approved by the FDA (DiMasi, 2001). Rather than purchasing an under-development product priced as a function of its probability of success, the inherent information asymmetry between sellers and prospective buyers knowledge of a product’s likelihood of success causes a lemons market to exist. Smaller, single-product firms are also more likely to advance failing products to later development stages than larger firms will be (Guedj and Scharfstein, 2004), further fueling the lemons market. By purchasing a portfolio of bundled compounds, the impact of purchasing a possible individual lemon is reduced. Further, for firms with portfolios consisting of several dozen compounds, the addition of a single product does not alter the shape of the pipeline as dramatically as the merger of two companies with similarly large portfolios. Acquiring the portfolio of products thus reduces the average transaction cost associated with acquiring individual products.
Hypothesis 2: The propensity for a pair of firms to merge will increase as the fit in their R&D development pipelines increases.

2.2 Drivers of organizational decision-making

As discussed in the introduction, managers are presumed to be capable of calculating the expected value associated with the consequences of their decisions with some degree of accuracy. Decision-makers, however, often make strategic choices associated with lower potential value creation than others. While agency theory holds that this situation results from managerial opportunism, it is also possible that managers are heterogeneous in their ability to estimate expected value accurately. Although market discipline should ordinarily serve as a mechanism to replace managers that are incapable of making or unwilling to make such calculations accurately, disciplinary mechanisms require that market participants (1) can observe managerial behavior and, more importantly, (2) can obtain (if they do not already possess) the power to influence that behavior (Flannery, 2001). When market participants are unable to observe or influence managerial behavior, the disciplinary power of market forces becomes reduced.

Indeed, extensive empirical evidence suggests that insulation from market discipline is associated with managerial ineffectiveness and lower performance. Increased takeover pressure and greater salience of market discipline correlates with greater improvements in performance and increased managerial turnover (Denis & Denis, 1995; Kini, Kracaw, & Mian, 2004; Mikkelson & Partch, 1997), and, conversely, restrictions to market discipline are associated with reduced
performance (Bebchuk & Cohen, 2005; Core et al., 2006; Gompers et al., 2003). Variation in governance practices that inhibit market discipline can cause heterogeneity in the level of managers’ ability or willingness to calculate expected value accurately because, without market discipline, incapable or effort-averse managers can remain in control of their organizations.5

A governance index was developed by Gompers, Ishii, & Metrick (2003; hereafter G-I-M)6, where governance is measured as the extent to which firms have bylaws or provisions in place which restrict shareholder rights. These provisions rose as a result of the 1980s hostile takeover market, where corporate raiders such as T. Boone Pickens and Ivan Boesky used junk bonds to acquire controlling stakes in publicly traded companies and instigate sudden and radical changes within those firms by replacing managers, breaking up conglomerates, and eliminating expenditures. Empirical evidence suggests that these takeovers (or even the mere threat of takeover) did provide efficiency gains in the early 1980s, but as overall efficiency rose, the continued use of leveraged buyouts eventually became associated with an increased the rate of default and bankruptcy (Holmström & Kaplan, 2001; Kaplan & Stein, 1993), causing firms and states to implement corporate bylaws7 and laws, respectively, to protect

5 This is not to say that managerial opportunism cannot also occur; it merely argues that managerial opportunism and managerial efficacy are both mechanisms through which insulation from market discipline can reduce firm performance.
6 A similar scale, proposed by Bebchuk et al. (2004) yields substantively similar results.
7 Such provisions included procedural restrictions on shareholder voting, financial protections for executives currently in place, or mandated delays, slowing down the acquisition process to make a hostile takeover using short-term financing untenable. With the fall of the hostile takeover market
organizations from corporate raiders that could destroy the company. A seemingly unintended effect of these laws, however, is that managers in firms with such restrictions in place become insulated from market discipline.

The G-I-M measure of shareholder rights restrictions, therefore, essentially measures the tendency of managers to be ineffective by virtue of their entrenchment. Firms with high shareholder rights restrictions are more likely to have ineffective management, where ineffective is defined as involving some combination of effort aversion, lack of capability and opportunism among managers. In such firms, the insulation from market discipline allows managers to remain employed even when they are less willing or capable of assessing the expected values associated with strategic options.

This logic leads to the following hypothesis involving the governance of an acquiring firm:

Hypothesis 3: Shareholder rights restrictions will attenuate the relationship between acquisition propensity and fit in (1) patent expiration schedules, and (2) product development pipelines. Firms with a high level of shareholder rights restrictions will be less likely to show a relationship between fit and acquisition propensity.

by the end of the 1980s, however, these provisions remained in place for most of these firms, despite the reduced necessity to ward off hostile takeovers.

8 This is not to say that managers who are ineffective or opportunistic would necessarily make decisions inconsistent with their firms' interests; it is only to say that, on the whole, the level of shareholder rights restrictions will be negatively correlated with the accuracy and certainty of estimations of expected value and the decisions implied by those estimations.
Note that the level of analysis associated with examining the effect of shareholder rights restrictions complicates the empirical analysis. While fit in patent expiration schedules or product development pipelines are traits endemic to a dyad, governance is a trait belonging to an individual firm. The distinction between the terms merger and acquisition, therefore, matter for this variable. When the decision to combine two firms lies wholly within one of those firms, as is the case in an acquisition, only the governance of the acquiring firm will impact the decision. Practically speaking, most combinations are acquisitions (even when publicly described as mergers) and true mergers-of-equals are actually quite rare (Wulf, 2004). Acquisitions are often referred to as mergers primarily for public relations purposes, to assuade negative reactions by employees or other stakeholders. Even when no acquisition premium is paid in a so-called pooling of-assets merger, or when an acquiring firm is re-named after the acquisition, asymmetry in the control of the merged company among managers of the two firms emphasizes the likelihood that one firm had disproportionate influence in the decision to merge. From the standpoint of empirical practicality, M&A research databases assign one firm in every combination to be the acquiror.

2.3 Circumstances affecting decision certainty

A high level of certainty presumes that decision-makers have all the information necessary to calculate expected values associated with their strategic choices. However, obtaining information has costs (March, 1994; March & Simon, 1958), so decision-makers must act on limited information (Cyert & March,
1963), increasing the uncertainty associated with their decisions. Less effective managers have less access to information, rendering their evaluations of strategic choices to be particularly uncertain. As uncertainty increases, organizations will tend to imitate organizations in their industry in an effort to appear rational (DiMaggio & Powell, 1983), with the hope that imitation of successful firms will lead to success for the imitating firm as well. Shared failure, if organizational practices conform, reduces the likelihood that managers of any one firm will be sanctioned for poor performance. As Keynes noted, “it is better for [one’s] reputation to fail conventionally than to succeed unconventionally” (1936: p. 158).

That being said, managers who imitate other firms’ actions inherently assume (or hope) that the circumstances driving others to pursue a strategic path are reasonably similar to the imitator’s own circumstances. In the context of mergers, where acquisition decisions are made based on the specific synergies between the acquiror and target firms, imitation of another firm may be a less beneficial heuristic for managers deciding what course of action to pursue, and providing a possible example of the circumstances in which value-destroying acquisitions occur. More substantially, since value creation opportunities vary at the dyad level, one can observe the extent to which a merger decision is based on the value creation opportunity or on other firms’ recently merger decisions.

Drawing on the work of DiMaggio and Powell (1983), Haveman (1993) argued that salience is the primary determinant of which actions will be copied. In the present context, the decision to merge immediately draws attention across
the mainstream business press, clearly increasing the salience of mergers and consequently increasing the likelihood that they will be imitated. Non-action, on the other hand, is not salient because it represents the status quo. Even if non-action leads to better performance, it is less likely to be imitated when there are more salient (but quietly unsuccessful) actors to imitate.

Once one firm merges, it increases the likelihood that others will follow as well. As a growing number of firms merge, the tendency for non-merging firms to follow suit increases as well (Granovetter, 1978). In this vein, mergers have historically exhibited wave-like properties (Rhodes-Kropf & Viswanathan, 2004; Stearns & Allan, 1996) similar to those exhibited by other management fashions (Abrahamson, 1996). This type of social influence can be measured as the prevalence (Carroll & Hannan, 1989; Hannan, Carroll, Dundon, & Torres, 1995) of other recent mergers in the industry. Prevalence can be measured in a variety of ways (i.e., count of mergers, dollar volume, etc.), but these measures tend to be highly correlated.

A recent review of institutional theory notes that the extent to which firms differ in their susceptibility to imitative pressures notes that “the central empirical contribution of institutionalist research to date—the consistent, impressive demonstration that context matters whether it be world polity or organizational field—has obscured the puzzle of when and how particular institutional mechanisms operate” (Schneiberg & Clemens, 2006). The literature largely states that the degree of susceptibility is proportional to the strength of the pressure perceived. Research has shown that such pressure can result from
social networks among executives (Davis & Greve, 1997), geographic proximity to other adopters (Pouder & St. John, 1996), historical contexts (Conell & Cohn, 1995), or the relative size of other adopters (Edelman, 1992). This logic is consistent with the notion that the recency of other mergers yields a positive main effect on the likelihood new mergers will occur.

As noted earlier, the degree of shareholder rights restrictions proxies the relative likelihood that decision-makers will calculate expected value accurately. Ineffective management would show a greater degree of uncertainty in estimating expected values, and have a greater tendency to look to other organizations as a cue to guide their behavior. Thus, when managers are insulated from market discipline, their propensity to imitate should be higher. That being said, an expected value estimated with a high degree of uncertainty can still dictate a logical course of action when the estimation is particularly high. For example, a firm believing that a merger has the potential to create somewhere between $10 million and $30 million of value will be more inclined to merge than one whose uncertain estimation ranges between a $10 million destruction of value versus a $10 million creation of value. Thus, firms with insulated managers will be particularly influenced by other recent mergers when fit calculations yield a moderate degree of fit rather than a high one. Firms with high shareholder rights restrictions will tend not to be influenced by other recent mergers when fit calculations are so high as to render the level of uncertainty to be irrelevant.

Thus, the mere existence of other recent mergers does not universally influence other firms to imitate those mergers. Indeed, following the Ciba-
Geigy/Sandoz and Glaxo/Wellcome mergers in 1996, Randall Tobias, the CEO of Eli Lilly, was quoted as saying, “Stakeholders of our company might reasonably ask: ‘When is Lilly going to join in this consolidation trend?’ I can tell you that our strategic intent is not to grow our earnings by a strategy of consolidating and then cutting out the redundancies we have created” (O'Malley, 1996). Astra CEO Haakan Mogren offered similar criticism, which is ironic given his own company entered into a merger agreement with Zeneca a few years later: “Looked at from the outside, I cannot understand why some of these mergers have been done… You mix old problems with new problems and you get drowned” (AFP, 1996).

Thus, a three-way interaction is proposed, as can be summarized in Figure 2.

\begin{center}
\textbf{Hypothesis 4:} The relationship between fit and acquisition propensity will be less pronounced for firms whose shareholder rights are restricted when the volume of merger activity the prior year increases.
\end{center}

3 Empirical analysis

3.1 Sample and data

The study population consisted of major firms in the pharmaceutical industry, defined as firms that, during the period from 1987 to 2004, controlled the patent rights of at least four unique products approved for usage by the U.S.
Food & Drug Administration (FDA), the government agency that evaluates and approves whether pharmaceutical products may be marketed by a particular manufacturer to address a specific medical condition, known as an indication. Given that the United States represents the largest market for pharmaceutical products, and given that all products must be approved by the FDA before they may be sold to the general public, I used the FDA’s publicly available database of approved products, known as the Orange Book to identify the universe of all compounds, with a unique product identification identifier containing information such as brand name, chemical compound name, manufacturer, dosage information, and, for products under patent protection, the patent expiration date.

Inasmuch as the Orange Book is continuously updated and reflects only a snapshot of the pharmaceutical market at the time of data collection efforts, I made a number of adjustments to the database to generate a set of product-year observations. I removed duplicate entries and non-patented products (beginning in the year following patent expiration) from the data set, and corrected product ownership in certain product-year observations for products whose ownership has changed, particularly for products whose rights are now controlled by a recently merged firm. Historical product ownership was validated by examining older copies of pharmaceutical reference books such as the Physician’s Desk Reference (1987-2004).

Data on product development was taken from NDA Pipeline (1987-2002), an annual survey of products under development that lists what products are
undergoing clinical trials, and whether these compounds are being tested at Phases I, II, or III. I used this information to identify, for each firm-year observation, the count of products at each phase of development. Data on acquisition activity was taken from Securities Data Corporation's (SDC) *Mergers & Acquisitions Database*, yielding a data set of 46,938 dyad-year observations, beginning with a population of 62 manufacturers in 1987, consolidating to 38 by 2004 through 26 acquisitions, as can be seen in Table 1. Data on financial control variables was drawn from *Compustat* and *WorldScope*.

Additional details regarding data collection processes can be found in Appendix I.

3.2 Methodological approach

The general approach utilized was a logit regression, where the dependent variable was coded as 1 if an acquisition was made, and zero otherwise. In a population of *n* firms, there are *n*(n-1) possible dyads of acquiror-target pairings in any given year. The propensity of whether firm A will acquire firm B and the propensity of whether firm B will acquire firm A were calculated as separate observations, but standard deviations were clustered across both years and “mirror images” of dyads. The unbalanced panel was examined as a pooled cross-section, in which each acquiror-target dyad had an observation for every year in the panel in which both firms existed. Since the observations are not independent
from each other, standard errors were clustered by dyad, which also alleviates the problem of double counting dyads. Since the clustering process automatically accounts for the lack of independence between observations over time, it also accounts for the lack of independence between dyads that are mirror images of each other.9

To conduct the empirical analysis, I listed all possible dyadic combinations between all firms in the population in a given year. This process was repeated for each year in the analysis, except that only dyads involving firms which existed in the population in that year could appear in the data set. This list of combinations was used to construct an event history for each dyad, in which a variable representing the merger received a value of “1” if the dyad actually merged, but a value of “0” if it did not.10

In addition to the independent and control variables described below, 3-year time period dummies were included. Single-year dummies would cause several years of data to be excluded from the analysis, because a year dummy for a year in which there were no mergers would perfectly predict a dependent variable that lacked variance. For purposes of regression analysis and calculation

9 In other words, I cluster dyad-year observations in which firm A can acquire firm B together with dyads in which B can acquire A. Clustering mirrored dyads separately yields identical results.

10 Given the relative infrequency of mergers across the population (representing approximately 0.06% of the total sample), I considered using rare-events corrections (King and Zeng, 2001). This approach essentially over-weights dependent variables of “1” in regression analysis, and helps to identify small effects that might not otherwise be detectable without collecting substantially more data, but is a controversial approach because the statistical process essentially samples on the dependent variable. Thus, the conventional logit model is a more conservative test because it treats all observations equally. All statistically significant variables in logit analyses remained significant in the rare events models, except that p-values were lower in the rare events logit models.
of interaction effects, expiration fit, pipeline fit, and log of lagged mergers were normalized to a mean of zero and a standard deviation of one.

3.3 Independent Variables

*Patent expiration schedule fit.* Fit associated with reducing the shocks of patent expirations was measured by examining each firm's product portfolio in a given year and the distribution of the future patent expirations of an acquiror and target combined. A portfolio consisting of products set to expire concurrently yields a greater shock to the firm than a portfolio consisting of products whose patent expirations occur steadily over a longer period of time. A pair of firms whose prospectively combined portfolios have a more steady schedule of expirations than either firm has individually is predicted to have a higher propensity of merging. This measure is computed by calculating the volatility of the distribution of future product expirations for the acquiror, target, and combined portfolio for each pair of firms in a dyad-year observation. Volatility was computed, for each dyad-year observation, as the coefficient of variation associated with future years' patent expirations. Fit is calculated as the ratio between the individual firms' values and value of the prospective combination: the higher the ratio, the greater the decrease in volatility attainable by merging, and the greater the fit between the two firms. More detail behind this calculation can be found in Appendix II, but a basic illustration of this calculation can be seen in Figure 3 (as well as Figure 1). Logarithmic transformation causes fit to become normally distributed.
Product development pipeline fit. For each firm-year observation, the NDA Pipeline provides information on the number of products under development and their developmental status—that is, whether they are in Phases I, II or III. In the absence of any clear standard for an optimal distribution of products across phases, I calculated the extent to which firms’ distribution of products across these phases is similar to that of the industry as a whole. Fit is measured as the extent to which a merger with a prospective partner brings the firm closer to this distribution.

Lagged mergers. As indicated earlier, the prevalence of social influence was operationalized by the volume of merger activity occurring in year \( t - 1 \) across the entire pharmaceutical industry, in dollars. Merger volume was operationalized using the dollar volume of total merger and acquisition activity in SDC (including acquisitions of smaller firms not present in the primary sample), and inflated to 2004 dollars using the Consumer Price Index. The values for lagged mergers were identical across each year of the analysis. Alternative operationalizations such as moving averages, multi-year lags, or using count data rather than dollar volume yielded materially similar results.

Governance. The G-I-M index, described earlier, was based on data collected by the Investor Responsibility Research Center (IRRC). This index was generated by examining a series of over twenty governance provisions that could
restrict shareholder rights. For each provision restricting shareholder rights, firms increased by one point on the governance scale.

A major shortcoming of the index is that it is only calculable for U.S.-based firms. Twelve of the twenty-six acquisitions in the sample were made by U.S. companies, potentially calling into question the generalizability of the results that follow. Non-U.S. companies were still included in the sample because (1) they could still be acquirors or targets, even without knowing the degree of shareholder rights restrictions, and (2) they enabled tests of fit-based hypotheses that were not dependent on the shareholder rights index.

3.4 Control Variables

_U.S.-based._ Three dummy variables were included to indicate whether a merger was U.S.-based: one if only the prospective acquiror was American, one if the prospective target was, and one if both firms were. When both firms are based in the same country, post-merger integration efforts are likely to be easier, suggesting that, holding other things constant, they are more likely to merge. Three firms in the sample, all Japanese, were based outside of the U.S. or Europe.

_Market capitalization._ Financial variables such as market capitalization, book value, cash, revenues and/or debt are all highly correlated, as they essentially serve as measures of firm size. Specifications controlling for any of them individually yielded similar results, so market capitalization alone was utilized to reduce multicollinearity associated with including multiple variables.
Larger firms were expected to tend to acquire smaller firms because it is more difficult for an acquirer to “digest” a relatively larger target (Hennart, 1988; Villalonga & McGahan, 2005). The logarithm of market capitalization was used in regression analysis.

*Market to Book (M/B) ratio.* Market to book ratio is the ratio between a firm’s market capitalization and its accounting value; a high market-to-book signals that the market believes that the firm will have high earnings growth (Fama & French, 1995), and is often used as a measure of a firm’s (or an industry’s) perceived ability to earn high returns to its capital. Firms with a higher M/B tend to acquire firms with lower M/B (Andrade, Mitchell, & Stafford, 2001; Jovanovic & Rousseau, 2002). The logarithm for target and acquirer M/Bs are used in regression analysis, because the ratio is skewed and truncated at zero and because doing so also enables one to test whether high M/B firms acquire low M/B firms. A positive regression coefficient for acquirer M/B coupled with a negative coefficient for target M/B is mathematically similar to regressing the logarithm of the ratio between acquirer and target M/B values without constraining the coefficients of the numerator and denominator to be equal (Edwards, 1995).

*Squared difference in M/B.* Rhodes-Kropf, et al. (forthcoming) argue that firms tend to acquire targets with similar M/Bs. The smaller the difference between prospective acquirer and target M/B, the more likely two firms will
merge\textsuperscript{11}. Squaring the difference between the M/Bs causes the regression to disregard which M/B is actually larger.

Target firm governance. Whereas managerial entrenchment in potential acquirors is hypothesized to affect merger propensity, a control for target firms' governance is also necessary. The major intention associated with restrictions in shareholder rights is to deter a firm from being acquired, suggesting a negative coefficient for this control variable. On the other hand, however, some empirical evidence has suggested that such firms are acquired anyway on the basis of the economic opportunity available to improve their underperformance (Singal & Singal, 2006).

A note on missing variables. Given the numerous sources from which data were collected, a number of variables had missing values for certain observations. Rather than discard these observations on a case wise basis, I made two adjustments. First, I substituted the mean value for the variable for any missing value. Second, I included a dummy variable coded as “1” associated with missing values in the regression analysis, in order to identify if firms with missing data were different from firms for which data was fully available. I also calculated interaction effects using the missing variable dummy.

\textsuperscript{11} This construct can also be examined as the ratio between acquiror and target M/B; the closer the ratio is to one, the more likely the firms will merge.
4 Results & Discussion

Descriptive statistics for data included in the analysis can be seen in Table 2, and Tables 3, 4, and 5 provide results for the logit models associated with the hypotheses in the present chapter.

Insert Tables 2 and 3 about here

Table 3 enables evaluation of Hypotheses 1 and 2. Model 1 presents a baseline model with only control variables included. The log of M/B squared is marginally significant in the negative direction, indicating the greater the disparity between acquiror and target M/B values, the less likely the firms will merge, consistent with Rhodes-Kropf et al. (forthcoming). Further, although the results are not statistically significant, the positive coefficient for acquiror M/B viewed together with the negative coefficient for target M/B is consistent with the view of Andrade et al. (2001) that high M/B firms tend to acquire low M/B firms. These results are particularly important, as they are all different measures in which the construct of fit predicts a main effect of whether firms will merge.

While one could postulate that a manager might actually use patent expiration schedules as a basis for merging, it seems far less plausible that a manager would deliberately use similarity in M/B ratios as a basis for merging as well.

The results also indicate a marginal propensity for acquirors to be based outside of the United States ($p < 0.10$), and a marginal propensity that, not surprisingly, firms of larger market capitalization are more likely to be acquirors
in this particular population, supporting the digestibility (Hennart, 1988) hypothesis \( (p < 0.10) \). The level of shareholder rights restrictions in the target firm, usually in place to hinder acquisition behavior, had no effect on acquisition propensity, with a beta of 0.06. Holmström and Kaplan (2001) have speculated that the type of restrictions measured by the G-I-M index protect against hostile acquisitions, rather than acquisitions in general (Singal & Singal, 2006). As the number of hostile takeover attempts plummeted from the 1980s takeover wave to the 1990s takeover wave, it is not surprising that there was no relationship between supposed acquisition protections and propensity to be a target. In sum, the results in the baseline model were directionally consistent with prior literature on merger propensity, and, in some cases, were statistically significant at the \( p < .10 \) level.

Hypotheses 1 and 2 posited that an increase in patent expiration schedule fit and product development pipeline fit are associated with an increased propensity for pairs of firms to merge. As can be seen in Table 3, Models 2 and 3, the coefficients for fit were significant \( (p < .05) \), such that a one standard deviation increase in the expiration fit score increases the odds ratio of merging by 52.6 percent and a one standard deviation increase in pipeline fit increases the odds ratio of acquiring by 23.6 percent. As these measures were uncorrelated, (see Table 2), it is not surprising that the results remained identical when both fit scores were included in the same equation, with or without the baseline control variables.
Table 4 contains regressions for testing Hypothesis 3, which indicated that managerial entrenchment would moderate fit: Non-entrenched managers would use fit as a basis for merger decisions, but entrenched managers would not use the fit score. The absence of a two-way interaction effect between product development pipeline fit and governance (Models 5 and 6) does not provide evidence to support the Hypothesis for the pipeline fit measure. However, the two-way interaction between patent expiration schedule fit and governance is statistically significant, with the level of significance a function of which other variables are included in the model. Simple slopes analysis, based on Model 7 and using methodologies recommended by Aiken and West (1991), verified the hypothesis. Among firms high in shareholder rights restrictions (one standard deviation above the mean), the coefficient for fit was not statistically significant ($\beta = 0.01, Z = 0.02, p = \text{n.s.}$). Among firms low in restrictions (one standard deviation below the mean), the relationship between fit and propensity was particularly high ($\beta = 1.49, Z = 2.42, p < .05$). Thus, for the patent expiration fit measure, Hypothesis 3 was supported.

Tests of Hypothesis 4 can be seen in the final table in the analysis. Similar to the results for Hypothesis 3, product development pipeline fit showed no moderating relationship with the variables (Models 3 and 4). The possibility
arises, therefore, that the particular operationalization of product development pipeline fit does not capture the subtler dynamics of how governance affects the ways product development pipeline information is used in acquisition decisions.

In analyzing the effect of patent expiration schedule fit, as can be seen in Table 5, Models 1 and 2, the three-way interaction between fit, lagged-mergers, and governance was significant (p < .01); this level of statistical significance remains robust no matter which control variables are included or excluded (tested in additional specifications not shown) in regression analysis. Given the significance of the three-way interaction term in Table 5, further analysis was necessary to determine the nature of the interaction and to identify its consistency with Hypothesis 4. Following Aiken and West (1991), a simple slope analysis was conducted in which governance was examined at high and low levels of patent expiration schedule fit and lagged mergers (i.e., one standard deviation above or below the mean value). Results of this analysis are plotted in Figure 4, and are consistent with the hypotheses described in Figure 2. When patent expiration stream fit is high (the rightmost columns in Figure 4, where each column consists of two bars in the bar chart), firms will merge, given the value creation opportunity presented by patent expiration stream fit. Differences between organizations of low and high restrictions of shareholder rights were not statistically significant (p > .30) within these groupings. The leftmost two columns, on the other hand, illustrate situations where managers considering an acquisition would be doing so in spite of a lack of fit between acquiror and target; that is to say, where the volatility of future patent expirations would worsen (or
improve very little) for a pair of firms that merge compared to their staying separate. In the absence of any social influence stemming from other firms merging, as seen in Column 1, firms will simply stay separate in deference to the lack of fit between them, with no effect for governance.

Column 2 enables testing of the primary Hypothesis of the present chapter. In this column, the low patent expiration schedule fit holds a firm should not acquire a prospective target, but with the recency of other major mergers in the industry, social influence to merge is high. Here, a main effect for shareholder rights appears ($p < .01$), such that firms with ineffective managers exhibit a significantly greater propensity to merge when fit is low than firms with high shareholder rights. These results support Hypothesis 4.

Figure 5 illustrates the results of the analysis in clearer detail. In this figure, the values for fit and lagged merger volume are placed in a scatter plot, with values mean-centered and standardized to the population of $\sim 40,000$ dyads. The points are identified as being associated with acquirors having low, high, or unknown shareholder rights restrictions. The distribution of the points is consistent with the hypotheses presented in the present chapter, clustered in four basic regions. High shareholder rights firms are found only in the right two regions, which represent areas where patent expiration stream fit is high. When fit is low, but mergers have a high level of prevalence (the upper left quadrant), only firms with high shareholder rights restrictions are found, representing
acquisitions that involving managerial opportunism or inefficacy. No mergers involving high shareholder rights firms are found in the upper left quadrant. No mergers involving firms of any governance level occur in the lower left quadrant, even though approximately 25% of acquiror-target observations map to that quadrant. For firms with missing values, even if the level of shareholder rights were to become known, they would have to map to the other three quadrants rather than the lower left. The absence of any mergers in that quadrant is consistent with the theory, even with missing information regarding a key variable.

The influence of other recent mergers on non-disciplined managers’ decisions to imitate them is consistent with empirical results presented by Carow et al. (2004), who argue that acquirors early in a merger wave outperform acquirors later in the same wave. In the present chapter’s theory, mergers that occur on the basis of fit, rather than on the basis of social influence, are more likely to create value, while mergers that occur on the basis of imitation, rather than on the basis of fit, would be less likely to create value. Carow et al. attribute their findings to first-mover advantages, arguing that first-movers are more likely to identify value-creation opportunities available due to asymmetric informational advantages over rivals. By contrast, in the present chapter, I argue that the appearance of a first-mover advantage for early acquirors exists because the population of early acquirors consists primarily of well-governed firms.
conducting acquisitions on the basis of value creation opportunities while the population of late acquirors includes poorly governed firms that conduct acquisitions as an act of imitation rather than due to the opportunity to create value. While Carow et al. argue (but do not empirically examine) that early movers have an idiosyncratic informational advantage, the present study suggests that early movement is due to a value creation opportunity idiosyncratically available to an early mover.

5 Contributions and Future Research

Much scholarly research on the subject of mergers and acquisitions has been motivated by the question of why mergers are so prevalent if, on average, they fail to create value for the firms involved. The present research draws attention to the original merger decision, and raises the possibility that value creation can be more clearly evaluated once the determinants of merger decisions are understood. Similar to the work of Haunschild and Miner (1997), it brings together social and economic explanations for strategic decisions, using heterogeneity in managerial capabilities to determine which factors drive strategic decisions.

This research parallels other work involving merger decisions (Danzon, Epstein, & Nicholson, 2004; Hall, 1999; Salis, 2006), except that instead of using the acquiring firm as the unit of analysis, I model acquisition propensity using the potential acquiror-target pair as the unit of analysis. I take this approach because of how value creation in acquisitions is ultimately defined: a situation
where the combination of two firms generates a net benefit compared to keeping the firms as separate entities. Thus, in contrast to much research on merger behavior, the present chapter examines merger decisions as a reflection of attributes of prospective acquiror-target combinations, rather than attributes of acquirors alone. Moreover, whereas the focus of this other body of work has been to establish a model in which endogeneity corrections alter interpretations of merger performance, the present chapter draws greater attention to the first-stage of this general model, presenting theoretical arguments for how fit, governance, and the presence of other mergers in the industry all impact the merger decision. A natural extension of the present chapter, therefore, is to determine whether models addressing corporate governance yield more consistent explanations for post-merger performance than previously proposed (Danzon et al., 2004).

While some studies examining merger antecedents acknowledge that firms self-select whether to merge, research on merger consequences tends to assume implicitly that no unobserved factors systematically differentiate merging from non-merging firms. If the assumption of no unobserved heterogeneity happens to hold true in a particular empirical context or theoretical angle, then the scholarly and practical implications associated with that research would, of course, remain unchanged. However, the existence of unobserved heterogeneity between merging and non-merging firms raises the possibility that studies of post-merger outcomes spuriously attribute performance effects to the merger decision, rather than to circumstances existing prior to the mergers. Endogeneity corrections may validate
findings in the literature on merger consequences, although it is difficult to predict in advance (Hamilton & Nickerson, 2003) which findings might be afflicted with endogeneity problems. The present chapter adds to this discussion by arguing a basis for which decisions are made, and lays the groundwork for future evaluation of whether the drivers of managerial decisions to merge or not merge affect whether value is created. In econometric terms, the particular methodology utilized allows for the calculation of merger propensity scores, which, in turn, can be used to control for endogeneity and evaluate whether merger outcomes are caused by mergers or are merely associated with them.

Indeed, research in the area of corporate diversification illustrates the importance of attempting to correct for endogeneity. Empirical analyses after the 1980s hostile takeover wave found that conglomerates receive lower market valuations (known as a “diversification discount”) than comparable groupings of separate, undiversified firms (Lang & Stulz, 1994). More recent analyses, however, have demonstrated that the diversification discount disappeared when econometric corrections for endogeneity were applied (Campa & Kedia, 2002; Villalonga, 2004), suggesting that the causal relationship between diversification and discounted valuation is spurious (see also Chevalier, 2004).

One critique of the present analysis is that the sample might appear to include only twenty-six observations, many of which have missing values for key variables, particularly for non-U.S. based acquirors. While this number of observations appears small, the analytical results are driven not only by the twenty-six mergers that did occur but also on data associated with the tens of
thousands of prospective mergers that did not occur. The number of positive observations is small because of the unit of analysis used and the infrequency of the phenomenon itself. Nonetheless, future research opportunities to extend the generalizability of these findings could consider domains of strategic choice in which the relative frequency of possible actions is less skewed.

Of course, the present study uses publicly available information to calculate fit, and managers of these particular firms would seem perfectly capable of doing the same. Support for these hypotheses relies on the assumption that publicly observable measures of fit are positively correlated with unobservable ones. If this measure of fit has low construct validity, then propensity calculations involving this measure become more noisy, and hence, more conservative. However, preliminary analyses (not shown) using other dyadic traits, such as those presented by Rhodes-Kropf et al. (forthcoming) points to findings consistent with those presented here. Finally, given that multiple measures of governance exist, some research has suggested that the adverse effects of shareholder rights restrictions can be attenuated by other governance mechanisms (Holmström & Kaplan, 2001; Kini et al., 2004).
References


Hopkins, J. 2005. Pfizer deal highlights growing value of biotech companies, *USA Today*: 5B.


Table 1. Distribution of firms, dyads and mergers in panel.

<table>
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<th>Mergers</th>
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</table>
Table 2. Means, standard deviations, and inter-item correlations for variables included in analysis.

|   | Obs | Mean   | SD   | 1    | 2    | 3    | 4    | 5    | 6    | 7    | 8    | 9    | 10   |
|---|-----|--------|------|------|------|------|------|------|------|------|------|------|------|------|
| 1. Acquisition | 46,938 | 5.54E-04 | 0.02 | --   |      |      |      |      |      |      |      |      |      |      |
| 2. Expiration fit | 46,938 | 0.18 | 0.36 | 0.012 |      |      |      |      |      |      |      |      |      |      |
| 3. Pipeline fit | 29,850 | 0.31 | 0.38 | 0.011 | -0.086 |      |      |      |      |      |      |      |      |      |
| 4. ln(Lagged Merger ) | 46,938 | 10.48 | 1.04 | 0.012 | 0.172 | 0.007 |      |      |      |      |      |      |      |      |
| 5. G-I-M index | 21,208 | 10.37 | 2.46 | 0.002 | 0.009 | 0.026 | 0.039 |      |      |      |      |      |      |      |
| 6. Market Cap ($B) | 39,061 | 19.91 | 32.76 | 0.021 | 0.174 | -0.035 | 0.345 | -0.106 |      |      |      |      |      |      |
| 7. Market to Book | 39,061 | 2.39 | 1.86 | 0.013 | 0.037 | -0.004 | 0.189 | -0.088 | 0.421 |      |      |      |      |      |
| 8. M/B diff squared | 32,566 | 0.13 | 2.42 | -0.005 | 0.021 | -0.013 | 0.112 | -0.038 | 0.148 | 0.336 |      |      |      |      |
| 9. Both Domestic | 46,938 | 0.28 | 0.45 | 0.001 | -0.033 | 0.000 | -0.001 | 0.000 | 0.041 | 0.156 | 0.033 |      |      |      |
| 10. US Based | 46,938 | 0.53 | 0.50 | -0.004 | -0.031 | 0.005 | 0.000 | N/A | 0.069 | 0.272 | 0.050 | 0.584 |      |      |
| 11. Year | 46,938 | 1994 | 4.88 | 0.012 | 0.231 | -0.014 | 0.765 | 0.054 | 0.453 | 0.242 | 0.156 | 0.000 | 0.001 |      |

G-I-M index refers to the index of shareholder rights calculated by Gompers, Ishii and Metrick (2003), and is only available for U.S. firms. A high value indicates a high degree of managerial entrenchment. Number of correlated observations is listed below each correlation value in the matrix.

\* significant at the 10% level
\*\* significant at the 5% level
\*\*\* significant at the 1% level
Table 3. Main effect models for fit measures.

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<tr>
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<th>(3)</th>
<th>(4)</th>
<th>(5)</th>
</tr>
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<tbody>
<tr>
<td>Expiration fit</td>
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<td>0.526</td>
<td>0.503</td>
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<tr>
<td></td>
<td>(0.373)</td>
<td>(0.219)</td>
<td>(0.211)</td>
<td>(0.270)</td>
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</tr>
<tr>
<td>Pipeline fit</td>
<td></td>
<td></td>
<td>0.236</td>
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<td>0.284</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>(0.116)</td>
<td>(0.117)</td>
<td>(0.120)</td>
</tr>
<tr>
<td>Tgt. G-I-M</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.067</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>(0.357)</td>
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<tr>
<td>Both Domestic</td>
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</tr>
<tr>
<td></td>
<td>(0.838)</td>
<td>(0.657)</td>
<td>(0.845)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Acq. US Based</td>
<td>-1.224†</td>
<td>-1.178†</td>
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<td>(0.657)</td>
<td>(0.655)</td>
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<tr>
<td>Tgt. US Based</td>
<td>0.794</td>
<td></td>
<td>1.158</td>
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<td></td>
</tr>
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<td></td>
<td>(0.682)</td>
<td></td>
<td>(0.738)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Acq M/B</td>
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<td>0.424</td>
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<tr>
<td></td>
<td>(0.374)</td>
<td></td>
<td>(0.386)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tgt M/B</td>
<td>-0.203</td>
<td>-0.183</td>
<td></td>
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</tr>
<tr>
<td></td>
<td>(0.176)</td>
<td></td>
<td>(0.173)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ln(M/B diff squared)</td>
<td>-0.138†</td>
<td>-0.135†</td>
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<tr>
<td></td>
<td>(0.071)</td>
<td></td>
<td>(0.071)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ln(Acq. Market Cap)</td>
<td>0.387†</td>
<td>0.373†</td>
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</tr>
<tr>
<td></td>
<td>(0.206)</td>
<td></td>
<td>(0.220)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ln(Tgt. Market Cap)</td>
<td>0.216</td>
<td>0.183</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>(0.155)</td>
<td></td>
<td>(0.156)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>(3.183)</td>
<td>(0.489)</td>
<td>(0.598)</td>
<td>(0.581)</td>
<td>(3.357)</td>
</tr>
<tr>
<td>Pseudo R²</td>
<td>0.090</td>
<td>0.036</td>
<td>0.046</td>
<td>0.057</td>
<td>0.122</td>
</tr>
</tbody>
</table>

N = 46,938. All models are logit regressions with a dependent variable of 1 for a merging dyad and 0 for a non-merging dyad. All models include dummy variables for five 3-year periods, with an omitted time period dummy variable for 1987-1989. Population means are substituted for variables with unavailable data; a separate dummy variable is included, not shown, was included for every main effect missing data, and every interaction effect involving a variable with missing data. All models are pooled cross sections; standard errors (in parentheses) are heteroskedasticity-robust and clustered by dyad.

† significant at the 10% level
* significant at the 5% level
** significant at the 1% level
Table 4. Models assessing interactions between fit and governance.

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<th>(1)</th>
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<th>(4)</th>
<th>(5)</th>
<th>(6)</th>
<th>(7)</th>
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<td>Expiration fit</td>
<td>0.531†</td>
<td>0.596†</td>
<td>0.709†</td>
<td>0.747†</td>
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<td></td>
<td>(0.220)</td>
<td>(0.338)</td>
<td>(0.375)</td>
<td>(0.393)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pipeline fit</td>
<td></td>
<td>0.235†</td>
<td>0.173</td>
<td>0.223</td>
<td>0.418</td>
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</tr>
<tr>
<td></td>
<td></td>
<td>(0.117)</td>
<td>(0.144)</td>
<td>(0.143)</td>
<td>(0.130)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Acquiror G-I-M</td>
<td>0.071</td>
<td>0.386</td>
<td>0.575</td>
<td>0.069</td>
<td>0.089</td>
<td>0.201</td>
<td>0.664</td>
</tr>
<tr>
<td></td>
<td>(0.421)</td>
<td>(0.480)</td>
<td>(0.532)</td>
<td>(0.412)</td>
<td>(0.413)</td>
<td>(0.423)</td>
<td>(0.474)</td>
</tr>
<tr>
<td>Acquiror G-I-M x Exp</td>
<td>-0.569*</td>
<td>-0.691†</td>
<td></td>
<td></td>
<td></td>
<td>-0.741</td>
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<tr>
<td></td>
<td>(0.315)</td>
<td>(0.369)</td>
<td></td>
<td></td>
<td></td>
<td>(0.356)</td>
<td></td>
</tr>
<tr>
<td>Acquiror G-I-M x Pipeline Fit</td>
<td>0.202</td>
<td>0.222</td>
<td>0.128</td>
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<tr>
<td></td>
<td>(0.164)</td>
<td>(0.161)</td>
<td>(0.147)</td>
<td></td>
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<tr>
<td>Target G-I-M</td>
<td>0.076</td>
<td>0.069</td>
<td>0.078</td>
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<td>(0.366)</td>
<td>(0.370)</td>
<td>(0.367)</td>
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<td></td>
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<tr>
<td>Both Domestic</td>
<td>1.335</td>
<td>1.368</td>
<td>1.323</td>
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<td></td>
<td>(0.878)</td>
<td>(0.839)</td>
<td>(0.882)</td>
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<tr>
<td>Acquiror US Based</td>
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<td>-0.834</td>
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<td>(1.408)</td>
<td>(1.453)</td>
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<tr>
<td>Target US Based</td>
<td>1.005</td>
<td>1.039</td>
<td>1.256†</td>
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<tr>
<td></td>
<td>(0.726)</td>
<td>(0.700)</td>
<td>(0.744)</td>
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<tr>
<td>Acquiror M/B</td>
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<td>(0.439)</td>
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<tr>
<td>Target M/B</td>
<td>-0.195</td>
<td>-0.204</td>
<td>-0.198</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>(0.174)</td>
<td>(0.171)</td>
<td>(0.165)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ln(M/B squared difference)</td>
<td>-0.143</td>
<td>-0.135†</td>
<td>-0.140†</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>(0.072)</td>
<td>(0.075)</td>
<td>(0.074)</td>
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<tr>
<td></td>
<td>(0.608)</td>
<td>(0.768)</td>
<td>(4.243)</td>
<td>(0.660)</td>
<td>(0.705)</td>
<td>(4.042)</td>
<td>(4.381)</td>
</tr>
<tr>
<td>Pseudo R²</td>
<td>0.036</td>
<td>0.044</td>
<td>0.110</td>
<td>0.046</td>
<td>0.054</td>
<td>0.121</td>
<td>0.143</td>
</tr>
</tbody>
</table>

N = 46,938. All models are logit regressions with a dependent variable of 1 for a merging dyad and 0 for a non-merging dyad. All models include dummy variables for five 3-year periods, with an omitted time period dummy variable for 1987-1989. Population means are substituted for variables with unavailable data; a separate dummy variable is included, not shown, was included for every main effect missing data, and every interaction effect involving a variable with missing data. All models are pooled cross sections; standard errors (in parentheses) are heteroskedasticity-robust and clustered by dyad.

† significant at the 10% level
* significant at the 5% level
** significant at the 1% level
Table 5. Test of three-way interaction between fit, shareholder rights and lagged mergers.

<table>
<thead>
<tr>
<th>Type of fit analyzed:</th>
<th>Patent Expiration Schedule</th>
<th>Product Development Pipeline</th>
</tr>
</thead>
<tbody>
<tr>
<td>ln(Lagged Mergers)</td>
<td>-0.266 (0.670)</td>
<td>0.076 (0.676)</td>
</tr>
<tr>
<td>Acquiror G-I-M</td>
<td>0.599 (0.484)</td>
<td>0.245 (0.493)</td>
</tr>
<tr>
<td>Fit</td>
<td>0.948** (0.349)</td>
<td>0.356 (0.221)</td>
</tr>
<tr>
<td>ln(Lagged Mergers) ×</td>
<td>0.989 (0.413)</td>
<td>0.242 (0.614)</td>
</tr>
<tr>
<td>Acquiror G-I-M</td>
<td>1.044** (0.403)</td>
<td>0.225 (0.614)</td>
</tr>
<tr>
<td>ln(Lagged Mergers) ×</td>
<td>0.355 (0.300)</td>
<td>-0.071 (0.194)</td>
</tr>
<tr>
<td>Fit</td>
<td>-0.718** (0.295)</td>
<td>0.161 (0.242)</td>
</tr>
<tr>
<td>Acquiror G-I-M × Fit</td>
<td>-0.761* (0.357)</td>
<td>0.207 (0.219)</td>
</tr>
<tr>
<td>Fit × Acquiror G-I-M</td>
<td>-0.505** (0.162)</td>
<td>0.068 (0.141)</td>
</tr>
<tr>
<td>ln(Lagged Mergers)</td>
<td>0.092 (0.385)</td>
<td>0.071 (0.394)</td>
</tr>
<tr>
<td>Target G-I-M</td>
<td>1.384 (0.920)</td>
<td>1.268 (0.842)</td>
</tr>
<tr>
<td>Both Domestic</td>
<td>-1.035 (1.497)</td>
<td>-0.670 (1.435)</td>
</tr>
<tr>
<td>Acquiror US Based</td>
<td>0.945 (0.805)</td>
<td>1.099 (0.726)</td>
</tr>
<tr>
<td>Target US Based</td>
<td>0.513 (0.447)</td>
<td>0.440 (0.429)</td>
</tr>
<tr>
<td>Acquiror M/B</td>
<td>-0.199 (0.174)</td>
<td>-0.217 (0.167)</td>
</tr>
<tr>
<td>Target M/B</td>
<td>-0.141* (0.074)</td>
<td>-0.136* (0.076)</td>
</tr>
<tr>
<td>ln(M/B squared difference)</td>
<td>-15.146** (4.570)</td>
<td>-7.223** (4.079)</td>
</tr>
<tr>
<td>Constant</td>
<td>-8.122** (1.043)</td>
<td>-15.196** (4.238)</td>
</tr>
<tr>
<td>Pseudo R²</td>
<td>0.070 (0.135)</td>
<td>0.067 (0.136)</td>
</tr>
</tbody>
</table>

N = 46,938. All models are logit regressions with a dependent variable of 1 for a merging dyad and 0 for a non-merging dyad. All models include dummy variables for five 3-year periods, with an omitted time period dummy variable for 1987-1989. Population means are substituted for variables with unavailable data; a separate dummy variable, not shown, is included for every main and interaction effect involving a variable with missing data. All models are pooled cross sections; standard errors (in parentheses) are heteroskedasticity-robust and clustered by dyad.
Figure 1: Conceptual logic behind fit as a driver of merger propensity.

Distribution of Patent Expirations for Firm A

Distribution of Patent Expirations for Firm B

Distribution of Patent Expirations for Firms A and B

The two firms combined will experience patent expirations on a more regular basis than either firm would alone, spreading the shocks out over time and facilitating more efficient use of firm-specific assets.
Figure 2: Summary of three-way interaction hypothesis:

<table>
<thead>
<tr>
<th>High volume of recent mergers</th>
<th>Low level of Fit</th>
<th>High level of Fit</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Merger decision contingent on governance:</td>
<td>Firms will <strong>merge</strong> (simultaneously supported by the both fit and social pressures)</td>
</tr>
<tr>
<td></td>
<td>• Managers insulated from market discipline will merge, imitating others' merger decisions</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• High shareholder rights firms will not merge, because market discipline would punish decision-making not consistent with the firms' interests</td>
<td></td>
</tr>
<tr>
<td>Low volume of recent mergers</td>
<td>Firms will <strong>not merge</strong> (mergers are unsupported)</td>
<td>Firms will <strong>merge</strong> (supported by fit)</td>
</tr>
</tbody>
</table>

Figure 3: Sample calculation of patent expiration schedule fit for dyad-year observation: Ciba Geigy – Sandoz

<table>
<thead>
<tr>
<th>Number of product patents expiring in...</th>
<th>Ciba-Geigy</th>
<th>Sandoz</th>
<th>Prospective Merger</th>
</tr>
</thead>
<tbody>
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<td>1997</td>
<td>1</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>1998</td>
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<td>1</td>
</tr>
<tr>
<td>2007</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>2008 or beyond</td>
<td>2</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>Total Products</td>
<td>6</td>
<td>5</td>
<td>11</td>
</tr>
<tr>
<td>Std Dev.</td>
<td>0.67</td>
<td>0.51</td>
<td>0.67</td>
</tr>
<tr>
<td>Mean/year</td>
<td>0.50</td>
<td>0.42</td>
<td>0.92</td>
</tr>
<tr>
<td>Coeff of Var</td>
<td>1.35</td>
<td>1.24</td>
<td>0.73</td>
</tr>
<tr>
<td>ln(Coeff of Var)</td>
<td>0.30</td>
<td>0.21</td>
<td>-0.32</td>
</tr>
</tbody>
</table>

**Fit score:**

\[
\ln \left( \frac{(CV_1 * CV_2)^{1/2}}{CV_{12}} \right)
\]

**Fit score:**

\[
\ln \left( \frac{(CV_1 * CV_2)^{1/2}}{CV_{12}} \right)
\]

\[
0.57
\]

\[12\] These firms indeed merged, changing their firm name to Novartis.
Figure 4: Results of Aiken & West (1991) analysis of three-way interaction between fit, lagged mergers, and shareholder rights.

![Diagram showing merger propensity for low and high lagged mergers, and low and high fit.]

Figure 5: Scatter plot of merging firms across population of all dyads.

![Scatter plot showing normalized distribution of actual mergers by governance.]

Low Fit  High Fit

Birds with high entrenchment

Low Lagged Mergers  High Lagged Mergers

Low Lagged Mergers  High Lagged Mergers

Low Fit  High Fit

Normalized distribution of Actual Mergers, by Governance

Low Restrictions  Unknown  High Entrenchment
Appendix I

A1. Data Collection Processes

A1.1 Patent Expiration Schedules

The FDA Orange Book represents the universe of all approved compounds, with a unique product identification number containing information such as brand name, chemical compound name, manufacturer, and dosage information for all pharmaceutical products ever approved, including discontinued products. For products under patent protection as of the date of my downloading the database, the patent expiration date was available as well.

Four major adjustments to the Orange Book data were necessary in order to create a panel data set reflecting annual historical snapshots of firms' patent-protected product portfolios. First, I retained only a single entry for each product, as some products appear multiple times in the database due to differing dosage sizes or formulations. Second, I converted the database from a one-time snapshot at the product level of analysis to a longitudinal data set at the product-year level of analysis, ranging from the years 1987 to 2004.

The third step was the least trivial. I removed product-year observations for years in which the product was either not yet approved or was no longer protected by a patent, sometimes causing a product's deletion from the database entirely, if its patent expiration was prior to 1987. For products whose patent expiration information was not available, I ascertained that patent protection
ceased once other manufacturers received approval to manufacture the same chemical compound, usually a number of years after the original manufacturer's approval. Typically, approval dates for the second, third, fourth manufacturer and beyond occur in reasonably close proximity to each other, further suggesting that the years between the first approval and the approvals for other manufacturers represent years of patent protection. For example, etoposide, a drug used to treat certain types of lung and testicular cancers, was first approved by the FDA for Bristol-Myers in 1983. The next manufacturer to receive approval for etoposide was Sicor pharmaceutical (a manufacturer with a reputation for manufacturing primarily generic products) in June 1995, followed by Bedford, Hospira, Pharmachemie and Supergen all within the next twelve months. I inferred, therefore, that etoposide was protected by patent for Bristol-Myers from 1983 to 1995, and deleted it in from the data set after 1995.

Following Danzon et al. (2004), I inferred that any product approved for more than 14 years was no longer under patent protection, since the typical pharmaceutical patent expires 17 to 20 years after clinical trials begin, and product approval typically occurs 3 to 6 years following clinical trials. (The lack of additional manufacturers for the product after patent expiration is usually a reflection of low demand for the product). I also excluded the less than two percent of the products that defined by the FDA as over-the-counter medications, since, even when protected by patents, they operate under different market elasticities than patented medications, which are primarily paid for by health insurers.
The fourth major change to the database reflected the fact that the *Orange Book* listed product ownership as of the date of database download and did not track transfers of product rights between manufacturers. Product ownership, therefore, had to be traced backwards in time. For all products controlled by firms that underwent a merger at any point during the sample frame, I looked up product ownership in older copies of the *Physician's Desk Reference* (PDR, 1987-2004). For example, the *Orange Book* lists Cutivate, a cream prescribed for eczema, as being controlled by GlaxoSmithKline, a firm whose existence was established through the merger of Glaxo Wellcome and SmithKline Beecham in 2001. The *PDR* indicates that it was controlled by Glaxo Wellcome prior to the 2001 merger, and by Glaxo prior to its own merger with Wellcome in 1995.

I also modified product ownership according to data listed in the *SDC Mergers and Acquisitions* database (described below) that indicated when a firm acquired or divested the ownership rights of a particular product or group of products. I also examined product ownership for a random subset of additional products currently belonging to firms that have not been involved in mergers or acquisitions and found that products change ownership relatively infrequently: less than 10% of all products changed ownership while under patent protection, excluding ownership changes directly associated with firm acquisitions. For purposes of the present chapter, I aggregated the data to the firm-year level and retained data only on firms that had at least four products in any one year during the years 1987 to 2004. The final data set indicated, for any given firm-
year, how many patented products a firm manufactured, and when patents for those products were due to expire.

A1.2 Product Development Pipelines

Data on product development was taken from _NDA Pipeline_ (1987-2002), an annual survey of products under development by major pharmaceutical firms. In order for a product to be approved by the FDA, the firm must demonstrate that the product safely and effectively treats a medical condition. This demonstration occurs through three phases of randomly controlled clinical trials: Generally, Phase I tests a product’s safety, Phase II examines its effectiveness in a few hundred patients, and Phase III extends the examination of efficacy to a few thousand patients.\(^{13}\)

For each product in Phases I, II, and III, I entered the year, product name, firm name, and phase into a spreadsheet. Because the _NDA Pipeline_ listed certain products as being in “Phase I/II” or in “Phase II/III” of development, these products were assigned as counting as 0.5 in each of the two phases. I assigned a product that was being developed for multiple indications simultaneously to the latest development phase listed among the indications; I ignored products that had already been approved other indications.\(^{14}\) Products

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\(^{13}\) See Trenter (1999) for a detailed discussion of the clinical development process.  
\(^{14}\) Firms are restricted by law from marketing products for any indication other than the one for which it has been approved, although physicians are not restricted from prescribing products to that indication, sometimes yielding discoveries of new potential indications for the product. A firm might thus conduct clinical trials even after a product’s first approval so that it can market the product for other indications.
whose development was jointly sponsored by two or more firms were repeated in
the sample for each firm associated with the development. I aggregated the drug
development data to the firm-year level to identify, for each firm-year
observation, the count of products at each of the three phases of development.

A1.3 Mergers and Acquisitions

Data on acquisition activity was taken from Securities Data Corporation's
(SDC) Mergers & Acquisitions Database. I queried the database to obtain
information on all acquisition deals between 1987 and 2004 involving firms
appearing in the Orange Book. Since the SDC database includes various types of
acquisitions not relevant to the present analysis, I ignored all transactions where
the deal was not actually completed, less than 20% of the target company was
acquired, less than 50% of the target company was owned after the transaction,
the value of the transaction was less than $100 million, or financial control
changed without substantive operational differences (such as a multinational
company changing the ownership structure of its subsidiaries for tax purposes, or
acquisition by a holding company whose actions were unrelated to product
development or patent expirations).

\[\text{\textsuperscript{15}}\] Data collection efforts for this variable are still in progress as of the time of this writing of the
manuscript. Actual data has been collected for all products under development in 1991, 1993,
1995, and 1998. I used this information to create a list of firms who had at least four products
under development at any single point in time, and then collected information for products under
development only for this list of major firms for the years 1989, 1994 and 1997. For the time
being, I used extrapolated product development information for major firms in the data for 1988,
I then examined the record for each transaction individually to identify those that represented acquisitions of entire firms versus acquisitions of specific assets such as manufacturing plants or product rights, and used the information on acquisitions of products to refine the Orange Book data described earlier. I assigned each acquisition as occurring in the year the merger was announced, even though the merger took effect at a later date, because merger decisions based on calculations of fit were likely to have been made on the basis of the company's status at the time of announcement. This process yielded a data set of 46,938 dyad-year observations, beginning with a population of 62 manufacturers in 1987 consolidating to 38 by 2004 through 26 acquisitions.

16 In general, about 5% of announced mergers are not actually executed.
Appendix II:
Detailed Descriptions of Fit Variables

A2.1 Patent expiration schedule fit: Variable construction

The value fit between expirations of product portfolios is based on the following set of calculations. The coefficient of variation associated with the anticipated patent expiration dates is used as a measure of the smoothness of patent expiration streams; the higher the coefficient of variation, the lower the smoothness. This coefficient is calculated as the variance across the count of patents expiring each year over a set number of years divided by the mean number of products expiring in each year. The coefficient of variation generated for each firm-year observation in the present study is based on the values for the number of patents expiring in each of the next twelve years; that is, each firm-year's coefficient of variation is based on the same number of values (twelve).

As described in the main body of the text, the ratio between the coefficient of variation associated with the dyad of firms and the average coefficient of variation (computed as the geometric mean) belonging to the two firms comprising the dyad determines the degree of fit (fit) found in the dyad. Logarithmic transformation of this ratio converts the distribution of the score to be approximately normal. Arithmetic transformation of the equation underlying fit, as seen below, illustrate that, like all ratios, it is unitless.
\[ \ln(FIT) = \left( \frac{1}{2} \left( \ln \left( \frac{\sigma_1}{\mu_1} + \ln \frac{\sigma_2}{\mu_2} \right) \right) \right) \ln \frac{\sigma_{12}}{\mu_{12}} = \ln \frac{\sigma_1}{\mu_1} + \ln \frac{\sigma_2}{\mu_2} - 2 \ln \frac{\sigma_{12}}{\mu_{12}} = \ln \frac{\sigma_{12}}{\sigma_1^2} - \ln \frac{\mu_{12}}{\mu_1^2} \]

Logarithmic transformation also permits a number of ancillary analyses associated with testing hypotheses regarding fit. Since the logarithm of a ratio is mathematically equivalent to the logarithm of the numerator minus the logarithm of the denominator, one can enter the components of the ratio as separate elements in statistical regression. Doing so can validate whether variance attributable to the numerator or the denominator predicts the dependent variable; not doing so, on the other hand, essentially constrains a regression model to assume an identical regression coefficient for the numerator and denominator (Edwards, 1994, 2001). Ancillary analyses in which regression models for fit comprised six independent variables (the natural log of the six unique elements in the equation above: the standard deviations of the dyad, firm one, and firm two, and the means of the product counts of the dyad, firm one and firm two), or two independent variables (the two quotients that follow the right-most equals sign in the above equation), or other similarly constructed independent variables all validated an important element of the hypothesis: Merger propensity is a function of the standard deviations of the distribution of patent expirations \((p < .05)\), controlling for the means \((p = n.s.)\). The means themselves (i.e., the number of products in each firm’s portfolio) are essentially included as a component of fit as a control variable, but do not themselves predict merger propensity in the regression analysis. Cash flow volatility is thus more safely operationalized by fit than it would be if this assumption did not
hold true. A single score for fit (rather than using multiple components to represent the construct) is utilized for model parsimony, particularly given the complexities of predicting a three way interaction where one of the constructs is represented by more than one variable.

One adjustment was made to the fit calculation that is not described in the main text. Because the stream of future patent expirations represent shocks to future cash flows, and because the net present value of distantly future cash flows is lower than the net present value of cash flows in the not-so-distant future, the values for future patent expirations must be discounted by the number of years into the future each product’s expiration will occur. Without such an assumption, fit would treat shocks occurring in the distant future as equivalent to shocks occurring in the near future, i.e., expirations occurring next year as being of equal importance to expirations occurring in ten years. Furthermore, such an adjustment lessens the importance of the number of years (twelve in the current model) used to determine the window of consideration for firms’ patent expirations, because very distant time periods become heavily discounted.

The denominator of the coefficient of variation calculation, therefore, consists of a weighted average of the counts of patents expiring rather than a simple average, with the weighting assigned as a function of each year’s value divided by a discount rate. The denominator is thus as follows:
\[
\text{Discounted Mean} = \frac{\sum_{t=1}^{12} n_t (1 - d)^{(t-1)}}{\sum_{t=1}^{12} (1 - d)^{(t-1)}}
\]

The parameter \( n \) represents the count of products expiring in a given year \( t \), the number of years in the future from the focal observation year. The assumed discount rate \( d \) is ten percent, one similar to that used by other researchers analyzing future revenues in the pharmaceutical industry (DiMasi, Hansen, & Grabowski, 2003 uses 11%; Gittins, 1996 uses 9%; Loch & Bode-Greuel, 2001 uses 10%). The numerator of the coefficient of variation calculation is similarly adjusted, although the calculation is made more complex by the nature of the standard deviation formula.

\[
\text{Discounted Standard Deviation} = \sqrt{\frac{\sum_{t=1}^{12} (1 - d)^{(t-1)} \times \left(n_t - \frac{\sum n}{12}\right)^2}{\sum_{t=1}^{12} (1 - d)^{(t-1)}} - 1}
\]

The coefficients of variation used to test hypotheses associated with fit, therefore, are based on the ratio of the discounted standard deviation to the discounted mean.

The calculation for fit otherwise assumes that each product is of equal value to a firm's future cash flows. While this assumption is certainly crude given the wide disparities in revenues that individual pharmaceutical products can generate, a more precise calculation would require collecting revenue data.
associated with every single product in the data set, which lies beyond the scope of present data collection efforts but may be included in future efforts.

A2.2 Product development pipeline fit: Variable construction

The variable of interest constructed to test Hypothesis 1 relies on different data than that collected to test Hypothesis 2, but utilizes a similar approach. For each firm-year observation, the *NDA Pipeline* provides information on the number of products under development and their developmental status, that is, whether they are in Phases 1, 2 or 3. Like Hypothesis 2, Hypothesis 1 posits that firms benefit from having an optimal distribution of the count of products across temporal categories: in the case of Hypothesis 2, the distribution is across years, while in the case of Hypothesis 1, it is across developmental phases. However, whereas the optimal distribution associated with Hypothesis 2 is that the number of products in each year’s observation is close to equal, the optimal distribution associated with Hypothesis 1 posits does not call for an equal number of products in each phase. In the absence of any clear standard for an optimal distribution of products across phases, I base my calculations on the assumption that firms desire a distribution is similar to that of the industry, and merge with prospective partners with the hope of coming closer to this distribution.

The coefficient of variation formula can be modified to accommodate this calculation. First, all constants can be removed from the equations for both the log of the standard deviation as well as the log of the mean. While inclusion of
the constants are important to interpreting the values associated with the mean, standard deviation, and coefficient of variation, their inclusion does not actually change the significance of coefficients in any regression results. Since every firm-year observation calculates a coefficient of variation on the basis of an identical number of components (12 years in the case of the patent expiration stream and 3 phases in the case of the R&D pipeline), components of the formulae that are based on the number of components can be removed as well. Additionally, discounting is not necessary in the model because it is not relevant to the product development process: The product development pipeline represents a snapshot of a firm's current state, rather than an anticipation of future activities. The denominator for remaining for the (former) coefficient of variation becomes simply the total number of products in the pipeline for a given firm; the numerator is reduced to the following equation:

\[
\text{Modified Standard Deviation} = \sqrt{\frac{1}{2} \left( \sum_{p=1}^{3} \left( n_p - \frac{\sum n_p}{\sum N_p} \right)^2 \right)}
\]

where the \( p \) identifies a specific phase, \( n \) represents the count of products belonging to a firm, and \( N \) represents the time-invariant count of products across the population. For a firm's products within a phase, when \( n_p \) is proportionately very close to the share of products in a phase within the population, the modified standard deviation yields a low value. For regression purposes, the modified standard deviation and the count of the total number of products in the pipeline are converted logarithmically and entered separately into the regression model.
The component of the model represented by $N_p/\sum N_p$ is the proportion of products in the population found in a particular phase. The data collected from the *NDA Pipeline* suggests a distribution of 22.8% Phase I drugs, 36.7% Phase II drugs, and 40.5% Phase III drugs across the sample. These estimates differ modestly from other estimates of the count of drugs across the research population. DiMasi and colleagues found that drugs in Phase I of development had a 71.0% probability of continuing to Phase II and a 31.4% probability of continuing to Phase III (DiMasi et al., 2003), and they estimate that the time spent in each phase ranges from 14.3 to 19.2 months for Phase I, 21.9 to 27.7 months for Phase II, and 36.8 to 38.5 months for Phase III (Kaitin & DiMasi, 2000). Combining the estimates for phase succession and time in phase suggests that, on average, the pipeline of the pharmaceutical industry contains approximately 32.9% Phase I drugs, 34.5% Phase II drugs and 32.6% Phase III drugs. The discrepancy between the estimates derived from DiMasi's work versus the estimate based on the *NDA Pipeline* data may result from the fact that DiMasi's calculations are based on project level data rather than firm level, and, more importantly, they reflect the pipeline mixture across the industry rather than within the population of large firms studied in the present chapter.

The theoretical basis of this measure is as follows: Consistent with business practices whereby large firms have a tendency to acquire early stage products under development from other firms (Higgins & Rodriguez, 2006), smaller firms not collected from (or not included in) *NDA Pipeline* are more
likely to develop drugs in earlier phases, and are often founded by scientists
discovering compounds with potential commercial use (Zucker & Darby, 1996).

Drugs in later phases require more extensive financial resources to undergo
clinical testing than early-stage compounds, so smaller firms with compounds
entering later phases must often partner with larger firms in the form of an
alliance or a single-product acquisition to complete clinical testing. Further,
Guedj and Scharfstein (2004) point out that larger firms are less likely than
smaller firms to promote marginally successful Phase I compounds to Phase II
because smaller firms are more reluctant to abandon their only viable candidates
while larger firms can abandon unpromising candidates in favor of other products
in their portfolios. Consequently, the NDA Pipeline data would show larger firms
as having a disproportionately high amount of later phase drugs under
development as compared to the industry data as a whole.

The ultimate question, therefore, is what is the optimal distribution of
products across developmental phases in an R&D pipeline for a major firm?
According to neo-institutional theory, firms uncertain of an optimal course of
action in an ambiguous environment will look at each other's behaviors and
imitate them in a process known as mimetic isomorphism (DiMaggio & Powell,
1983). This process of imitation will occur for two reasons. First, the process of
searching for an optimal solution can be complex in light of the ease of imitation
(Cyert & March, 1963). Second, normative behavior is seen as more legitimate
than behavior that deviates from the population, so organizations that act
normatively are able to acquire resources and maximize their survival more
effectively than deviating organizations (Meyer & Rowan, 1977). The optimal
distribution across developmental phases in an R&D pipeline for major firms,
therefore, is likely to be somewhat stable over time and across a population of
similar firms.

One can therefore compare the distribution of products under development
in an individual firm compared to the distribution of products belonging to what
that firm would look like if combined with a merger partner. Two firms are
complementary in their product development positions if one firm's deficiency of
products in a Phase can be counterbalanced with a partner's surplus in that same
phase of development.
II. Doctors, $$ and Drug Development:  
The Rise of For-Profit Experimental Medicine

Abstract

Over the past 15 years, academic medical centers have ceased to be the primary locus of industry-sponsored clinical trial activity. Instead, clinical trials have increasingly been conducted in private practices and for-profit, dedicated study sites. We examine the underlying causes of this startling evolution. On the demand side, the greater availability of non-academic investigators has enabled pharmaceutical firms to better match physicians' skills with specific projects. On the supply side, we argue that the growth of managed care health insurance has contributed to a rise in the number of non-academic physicians performing clinical research. We find evidence consistent with these claims using a unique data set containing information about 85,919 site contracts for 7,735 clinical trials between 1991 and 2003. Furthermore, we examine the gap in prevailing prices for comparable procedures conducted for clinical trials versus conventional medical care, and conclude that the effect of managed care on entry is consistent with non-academic physicians “inducing demand” so as to resist downward pressures on their income.

*This chapter was co-authored with Pierre Azoulay.*
1 Introduction

Physicians invest in human capital through long years of training in medical school, residency, and clinical fellowship. During the routine provision of medical care, most physicians apply their human capital narrowly, in ways that generate mostly private returns — both to themselves and to their patients. This very same human capital, however, can also be deployed in ways that generate social returns, during the conduct of clinical trials sponsored by public research institutions or by pharmaceutical firms. Clinical research could generate contemporaneous spillovers on the health of private patients treated by physicians who also treat experimental patients; and it certainly generates spillovers on the health of future patients, through advances in useful medical knowledge.

Borrowing from the vocabulary of the endogenous growth literature (e.g., Romer 1990), the present chapter examines the demand and supply forces that shift skilled medical personnel from the “production sector” of the medical care economy — routine care — to its “ideas sector” — participation in clinical research.

The clinical research industry emerged in response to regulatory requirements for the development of new pharmaceutical compounds. In order to gain approval for market introduction, the United States Food and Drug Administration (FDA) and its foreign equivalents require that a pharmaceutical company provide substantial evidence of a drug’s effectiveness, through adequate and well-controlled clinical investigations. Although the precise requirements have evolved over the years, proof of effectiveness must generally be demonstrated by the
results of randomized controlled trials (RCTs). In contrast to early-stage drug
discovery research, which are often conducted in in-house laboratories,
pharmaceutical firms contract out the conduct of experimental human studies to
independent physicians called clinical investigators. Traditionally, most clinical
investigation was conducted by physicians employed in academic medical centers or
community hospitals. Since the early 1990s, however, academic organizations have
gradually ceased to be the primary locus of industry-sponsored drug development
activities. Instead, clinical trials have been taking place outside academic
institutions: independent hospitals, private practices and for-profit, dedicated
clinical research sites. During the 1990s, the proportion of academic clinical sites
decreased steadily from 70% of U.S. sites in 1991 to 35% in 2001, as can be seen in
Figure 1. The present chapter seeks to provide a comprehensive examination of the
underlying causes of this startling evolution.

In a first step, we focus on the role played by the level of demand for clinical
trials by the pharmaceutical industry. Specifically, variation in project
characteristics leads to variation in the relative importance of doctors' effort on two
tasks that compete for their attention: data production — the routine manipulation,
storage, and transfer of symbolic information within established categories; and
knowledge production — the establishment of novel conceptual categories,
hypotheses, and causal associations (Osberg, Wolff, and Baumol, 1989).
Pharmaceutical firms fine-tune the mix of academic and non-academic investigators
to achieve a desired skill mix for each project. This implies that the proportion of
academic investigators at the project level should correlate with variables that
proxy for the importance of knowledge-production activities, relative to data-production activities.

On the supply side, we argue that the growth of managed care health insurance has been a strong impetus for entry into the clinical trials industry. Under managed care, health insurers took a more active role in attempting to reduce health care costs (and thus, the price of insurance policies) through a variety of financial mechanisms. These mechanisms were designed to mitigate the moral hazard inherent in insurance itself and to leverage the market power of health consumers as a collective body to lower prices paid for medical services. A perhaps unintended consequence was that these mechanisms also adversely affected the earnings of medical service providers (Hadley and Mitchell, 1999).

Physicians, in response, have sought alternative sources of compensation, conducting clinical trials instead of providing traditional patient care because payments from pharmaceutical firms were more in line with the cost-plus arrangements characteristics of traditional indemnity insurance. However, the incentive to substitute experimental patients for private patients is muted in academic medical centers, since academic physicians are typically not full residual claimants on these incremental profits. Moreover, cooperating with industrial firms often carries a stigma in the academic setting, because participating in clinical trials involves relinquishing some degree of intellectual autonomy to the sponsor. This argument implies that “for-profit” clinical trial activity should be highest in areas of high managed care penetration, but that this correlation should be smaller or zero in the case of academic doctors.
We use a variety of data sources to support our argument. The primary dataset consists of 85,919 clinical trial contracts granted between 1991 and 2003 collected by Fast Track Systems, Inc. In a first step, we aggregate the data up to the clinical trial level to show that the fraction of academic investigators correlates with indicators of knowledge intensity, such as different measures of compound novelty, whether the trial takes place in an inpatient setting, and project phase. In a second step, we collapse this same source of information so as to exploit cross-sectional and longitudinal variation in the volume of clinical trials activity across geographic areas — counties or Health Service Areas (HSAs) — and show that high managed care penetration in an area is associated with higher levels of "for-profit" clinical research activity in that area, but bears little relationship with the volume of academic clinical research.

In a final step, we attempt to distinguish between two mechanisms that could underlie the relationship between managed care and clinical research volumes. The growth of managed care penetration is often alleged to have raised physicians' incentives to practice medicine in groups, in part to gain negotiating leverage with insurers (Casalino, Pham and Bazzoli, 2003). As a byproduct, medical groups often invest in information technology, and these same IT investments could in theory lower the costs of entry into clinical research. In contrast, the demand inducement explanation we favor does not imply that large practices be more prone to enter the research arena, but is critically dependent on the existence of rents earned by physicians on experimental patients. We adjudicate between these two competing explanations in two ways. First, we show that small group practices (less than ten
physicians) are driving the correlation between “for-profit” research and managed care. Second, we make use of a separate dataset supplied to us by RapidTrials, Inc. containing payment data for 1,227 medical procedures conducted at clinical research sites from 1997 to 2004. We compare the prevailing price paid by clinical trial sponsors for these medical procedures to the Medicare fee schedule for those same procedures, and find that clinical investigators earn two to three times more on average from pharmaceutical sponsors, relative to Medicare.

The rest of the paper proceeds as follows. In the next section, we present a brief overview of clinical development and of the trends that have affected the clinical trials industry. Section 3 provides a similar overview of managed care and its effects on physician behavior. Section 4 describes the data, modeling approach, and identification strategy. Section 5 presents the main econometric results, while Section 6 offers some concluding remarks.

2 The Rise of For-Profit Clinical Research

2.1 Historical context

Clinical development is a complex, time-consuming, and costly process, as experimental studies demand careful coordination of activities across scientific disciplines, organizational and institutional boundaries, and, occasionally, countries. Following the synthesis of a new molecule and animal toxicology studies, drug companies must file Investigational New Drug applications (INDs) with the Food and Drug Administration (FDA) in order to obtain the necessary authorization for testing the compound’s efficacy in treating a particular ailment, known as an
"indication," in human trials. The development process has a substantial risk of failure: Conditional on filing an IND, the probability of eventual regulatory approval hovered slightly above 20% in the early 1990s (corresponding to a cohort of 1979-1983 INDs; DiMasi, 1995). Once the clinical phase is completed, companies submit New Drug Applications (NDAs) to the FDA and regulatory review begins, during which the firm’s medical experts present the agency with evidence for the product’s safety and efficacy, as gathered from clinical trials. This process typically involves a period of four to eight years between the filing of the IND and approval of the NDA (DiMasi, Seibring, and Lasagna, 1994; Kaitin and Healy, 2000).\(^1\)

Prior to 1962, the FDA routinely considered evidence of efficacy as part of the drug approval process, but this evidence was usually limited to casual observations from practicing physicians (Quirk, 1980: p. 197). A major scandal (the 1961 thalidomide disaster, in which a drug marketed for the treatment of morning sickness was later found to cause severe birth defects) and the rise of the consumer protection movement gave the impetus to the adoption of the 1962 Kefauver Harris Amendment. This Act of Congress required that every new drug be approved prior to its marketing, and that this approval depended on the drug’s being proven safe as well as effective. Further, the Act established a legal framework for the subsequent use of randomized controlled trials (RCTs) as the “gold standard” in clinical research. In addition to this substantive change, the FDA used its discretionary

\(^1\)While the FDA has dramatically reduced the time needed to evaluate NDAs following the Prescription Drug User Fee Act (PDUFA) of 1992, this has been offset by a comparable increase in the length of the clinical phase. For 67 new chemical entities approved by the FDA in 1993, 1994 and 1995, the mean length of the clinical phase (IND filing to NDA submission) was 7.1 years; for the approval phase (NDA submission to approval), it was 2.0 years (Kaitin and Manocchia, 1997).
power to influence the procedures according to which pharmaceutical companies would collect clinical data, produce evidence, and determine marketing strategies. The Kefauver Harris Amendment thus led to a proliferation of administrative rules that significantly raised the costs of drug development (Peltzman, 1973; Thomas, 1990). Testifying to the importance of these formal requirements is the extraordinary quantity of information processing necessary for regulatory review: A complete NDA may contain up to 200 volumes of information (Quirk, 1980).

Long before formal testing requirements became enshrined into law, pharmaceutical companies contracted experimental human studies to be conducted by clinicians employed outside the organizations. Pioneering examples of such collaborations include that of the Eli Lilly corporation and the University of Toronto for the development of synthetic insulin in the 1920s, and that of Merck with University of Pennsylvania researchers in the 1930s for the development of the anesthetic Vinethene (Swann, 1988). The growing use of academic researchers in this capacity reflected three major underlying phenomena: the rapid advances in the fields of physiology and pathology in the early part of the twentieth century, which formed a solid scientific foundation for clinical investigation (Harvey, 1981); the emergence of the modern medical school and its affiliated teaching hospital as a distinct research institution (Rothstein, 1987); and the birth of a new profession, that of the full-time clinical professor (Fye, 1991). Clinical trials are thus conducted by physicians, known as clinical investigators, who are located across different research sites. Trials typically make use of multiple research sites and physicians
both to accelerate the product development process and to alleviate the possibility that results might be attributed to a particular research site or physician.

Clinical investigators operate out of a variety of different research sites, including academic medical centers, community hospitals, private practices, and for-profit clinical testing organizations. The proportion of academic clinical sites decreased steadily over time, but still represented over 70% of U.S. sites as late as 1991. That number shrank to a mere 35% by 2001, according to industry sources (Hovde and Seskin, 1997; Zisson, 2001). There are two broad classes of explanations for this shift that focus, respectively, on the demand- and supply-sides of the market for clinical investigators.

2.2 Demand-side considerations

The academic and non-academic sectors differ in the relative emphasis put on knowledge production (versus data production) by clinical investigators. In addition to conducting industry-supported clinical trials, academic investigators also carry out "basic" clinical investigations, which are rewarded by publications, N.I.H. grants, academic prestige, and promotion. In contrast, at commercial sites, investigators' allocation of effort within clinical trials is not lured away from data production by competing incentives. This diversity provides pharmaceutical firms with the ability to match the composition of the investigator team with the needs of the clinical study. For example, when the study examines a more established scientific hypothesis, the objectives of investigators in the commercial sector will be more aligned with sponsors' interests. By contrast, when hypothesis generation is
more valuable or when the product team "is ignorant about what it is ignorant about," then encouraging investigators to follow their scientific intuition might become comparatively more valuable. According to this view, the mix of academic and non-academic investigators results from a process by which the pharmaceutical companies match investigators of various type and projects with heterogeneous characteristics (Azoulay, 2004).

If changing preferences of pharmaceutical companies or changing FDA requirements have increased the number of data-intensive projects, relative to the number of knowledge-intensive projects, then this shift could account for part of the observed growth. A number of reports have emphasized the increasing prevalence of "me-too" drugs in corporate R&D strategies (e.g., NIHCM, 2002). But these analyses only pertain to the characteristics of approved drugs, and as we will document later, we do not find evidence of a shift towards incremental projects in our data, which includes trials pertaining to drugs that eventually secure FDA approval as well as drugs whose development is still in progress or has been discontinued. Moreover, the ranks of non-academic clinical investigators have swelled with such celerity that it seems unlikely that demand-side phenomena could have completely determined the emergence of for-profit experimental medicine. In particular, explanations that stress variation in project characteristics beg the question of why pharmaceutical firms were not purposefully matching physicians with projects in the earlier period. Geographic variation in the extent of entry of for-profit investigators suggest that supply-side forces were also at work.
2.3 Supply-side considerations

We view RCTs as an innovation that any doctor is “at risk” of adopting at any particular point of time. The overall stock of potential investigators has increased over time, as medical school curricula increasingly came to emphasize that RCTs provide the standard upon which sound clinical decision-making should be based. Moreover, beginning in the late 1970s, the FDA began a decade long effort to codify what had heretofore been informal agency practice. Culminating in the 1987 “IND/NDA rewrite,” the new regulations added or clarified requirements for monitoring, record keeping, adverse event reporting and designing Phase II and III studies in return for greater flexibility during safety testing (Sobel, 1988). In general terms, the regulations caused the agency to become more deeply involved in process-related issues than had previously been the case. This massive codification effort may have made it easier for non-academic physicians to learn how to conduct clinical trials, exogenously lowering the costs of adoption and enabling them to incorporate clinical research into their traditional practices. A more satisfying explanation for the rise of for-profit experimental medicine, therefore, starts from the observation that the supply of non-academic investigators was likely constrained until the late 1980s. The cumulative effect of new cohorts of physicians familiar with RCTs and the procedural templates provided by the IND/NDA Rewrite relaxed this supply constraint and allowed pharmaceutical firms to draw from a more substantial population of non-academic investigators to match with their
projects. This explanation, while supported by anecdotal evidence, does not lend itself to empirical testing since it is essentially a slow-moving population-level trend.

We focus instead on a different supply-side explanation: the rise of managed care health insurance. In recent decades, managed care has created downward pressures on physicians' personal incomes and reduced the utility they gain from practicing traditional patient care. Affected physicians, in turn, have been more likely to substitute "experimental patients" for their traditional patients.

3 Managed Care and Its Effects on Physician Behavior

Managed care refers interchangeably to a set of health insurance products and to an approach to medical decision-making that gained wide prevalence in the U.S. healthcare environment during the 1980s and 1990s.² It is a general term used to describe a variety of mechanisms through which health insurers seek both to control costs and to improve or maintain the quality of medical care for their policyholders. The distinguishing features of these mechanisms are usually some combination of the following: (1) selective contracting, whereby payers negotiate prices (often unilaterally) in the form of a "fee schedule" and selectively contract with a limited number of healthcare providers in a given locale; (2) monetary and non-monetary incentives that steer health consumers towards the selected providers; (3) utilization reviews and controls that restrict providers' medical decisions, especially for more expensive medical procedures; and (4) the assumption of some

²See Glied (2000) for a review.
financial risk by physicians in the form of capitation contracts. In combination, these features have generally reduced the cost of health insurance compared to indemnity policies, in which physicians are paid on a cost-plus basis.

It was only in the 1980s that the number of patients enrolled in managed care plans increased above nominal levels, due in part to the passage of the HMO Act of 1973, which required certain types of employers to make HMOs available as an employee benefit. The growing prevalence of managed care gave health care providers little choice but to contract with managed care insurers or risk losing patient volume: By 1995, over 80% of physicians had contracts with at least one managed care organization (Emmons and Simon, 1995). The vast majority of patients are now enrolled in some type of plan that falls under the umbrella of managed care (Jensen, Morrisey, Gaffney, and Liston, 1997). Even today, however, managed care penetration varies widely across geographic areas, with concentration highest in California (Glied, 2000).

A large number of studies (e.g., McLaughlin, 1987; Miller and Luft, 1997) have examined the impact of managed care on health outcomes and expenditures, although evidence regarding the ability of managed care to alter the practice of medicine has been more limited. Baker (1997; 1999) found that managed care lowers medical expenditures not only by controlling costs for managed care patients but also by decreasing the revenues physicians receive for services rendered to patients not subject to managed care and its incentive-based contracts — i.e., the indemnity and fee-for-service (FFS) patient populations. Several spillovers mechanisms between managed care and non-managed care patients also make it
empirically more difficult to isolate their effects. First, managed care’s presence in a geographic area creates a more competitive environment overall for the prevailing market prices charged for medical procedures. Second, managed care reduces the incentive (and available revenue) for physicians to invest in higher-cost technologies, affecting the technology’s availability and the subsequent likelihood that physicians will utilize it with their non-managed care patients. Finally, managed care spreads conservative behaviors and practice patterns, such that an indemnity or FFS patient becomes less likely to receive a more expensive treatment than an equivalent managed care patient, lest the physician be perceived as making a decision on the basis of reimbursement level rather than on the basis of medical need. This general argument also finds support in the research conducted by Glied and Zivin (2002), who show that drug prescribing patterns converge as a greater proportion of a physician’s practice consists of managed care patients.

Despite numerous efforts to document an effect of managed care on the income of physicians, such studies have been far from conclusive (Clark and Thurston, 2000; Hadley and Mitchell, 1999; Luft, 1999; Simon, Dranove, and White, 1998). In part, this reflects the lack of a credibly exogenous source of variation to identify the effect of managed care penetration: Managed care organizations may be more likely to pursue market entry in areas in which medical expenditures (of which physician income is a substantial component) are already high or expected to increase. But the lack of a consistent effect on physician income could also reflect demand inducement or “target income” behavior on the part of physicians, whereby physicians respond to fee cuts by increasing the volume of services provided. In
recent years, evidence has accumulated that this type of behavior indeed explains
the limited success of large health care payers such as Medicare in lowering
expenditures through reductions in scheduled fees (Gruber, Kim, and Mayzlin,
1999; Gruber and Owings, 1996; Leape, 1989; Yip, 1998).³

This body of research builds on a general model of physician behavior
proposed by McGuire and Pauly (1991), who demonstrate that target income
behavior often alleged to characterize physicians' decisions is not necessary for
demand inducement to take place. Moderately strong income effects are sufficient,
and the strength of income effects is the key determinant of a physician's volume
response to a reduction in fees. They also emphasize that, in the presence of
multiple payers, multiple avenues exist for recouping income shortfalls. The extent
to which physicians will substitute non-managed care patients for managed care
ones depends on the relative ease of inducement, the sensitivity of demand to
inducement, and the relative payment for services in each market.

McGuire and Pauly (1991) motivated their model by considering the
introduction of the Medicare Fee Schedule in 1992, and its impact on the volume of
procedures performed on behalf of non-Medicare patients. We argue that this
general model can apply to the case where the payers of interest are not multiple
insurers but instead, more broadly, multiple types of revenue sources: namely,
managed care insurers and pharmaceutical firms, who pay for the medical services
provided to patients enrolled in the clinical trials they sponsor. Indeed, recent

³Some policymakers have consequently incorporated demand inducement assumptions into fee
schedule adjustments, relying on the expectation that physicians will offset a portion of losses from
fee reductions by increasing the volume of services provided (Physician Payment Review Commission,
survey evidence suggests that “physician entrepreneurialism” — of which clinical trials is a prime example — is associated with high managed care penetration and other financial pressures (Pham, Devers, May, and Berenson, 2004). This substitution between patient types (rather than between payer types within the traditional patient category) occurs as a response to the gap in the relative payments between payer types.

What remains to be explained is why patterns of substitution between patient care and clinical research might differ between the academic and non-academic sectors. The main distinction between academic investigators and their colleagues in private practice lies in the relative strength of the explicit output incentives they face. Pharmaceutical companies routinely provide bonuses and other financial enticements to clinical investigators for meeting or exceeding enrollment targets. However, academic institutions prohibit such financial incentives because of the potential conflict of interest they create between the patient and the physician. Even in the absence of such restrictions, academic physicians are not full residual claimants on the additional revenues generated by clinical trials; that said, such funds do provide a valued source of financial support that supplements basic research.

In addition, and perhaps more importantly, participating in industry-sponsored clinical trials has been a source of stigma among clinical faculty in academic medical centers. Whereas basic research makes unique demands on the

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4 We do not mean to suggest that clinical trials are the only way for physicians to generate revenues beyond the treatment of ordinary ailments and injuries. Preudenheim (1996), for example, speculates that the increased marketing of and consequent demand for expensive elective cosmetic procedures is a direct consequence of managed care as well.
creative and scientific insights of the investigator, clinical trials — especially
data-intensive ones — imply a substantial relinquishing of intellectual autonomy to
the sponsor, since the investigator must adhere to an agreed-upon research protocol
likely to have been designed by someone else. As a result, clinical trials do not
produce rewards commensurate with those brought by other academic activities,
such as publications and NIH grants, let alone intellectual satisfaction. Thus, we
argue, not only will more clinical trial activity take place in high managed care
penetration areas, but also this effect should be especially pronounced among
non-academic investigators.

Besides demand-inducement in a multiple-payer context, an association
between managed care penetration and clinical trial activity across geographic areas
could be observed for technological reasons, independent of substitution incentives.
As managed care insurers have increasingly leveraged their market power against a
diffuse body of physicians, those physicians, in turn, have tended to aggregate into
larger group practices (Casalino et al., 2003; Casalino, Pham, and Bazzoli, 2004).
These large practices, having gained negotiating leverage, have also taken advantage
of scale economies to invest in technologies such as electronic recording of patient
information and diagnostic imaging equipment. These sunk assets are relevant to
our argument, since they could be deployed to support the infrastructure needed to
be productive in the realm of clinical research. The relevance of the scale rationale
for entry can be examined empirically, since it implies that, among physicians in
private practice, those practicing in large groups should drive the observed
association between managed care and clinical trials volume.
4 Data and Methodological Considerations

4.1 Data sources and sample construction

We make use of several data sources to conduct our analysis. The first data source is a proprietary data set of clinical investigator contracts made available to us by Fast Track Systems, Inc. Since the late 1980s, Fast Track has collected detailed information on clinical research from clinical trial sponsors. It then analyzes and aggregates this information for subscribing organizations to help them plan budgets and negotiate clinical research contracts with investigative sites. While no company can be identified by name due to confidentiality agreements, the data collected represent a substantial share of the global clinical research industry. The data set used for the present analysis includes 7,735 clinical trials conducted by 69 firms involving 1,912 clinical compounds and 85,919 research sites for studies conducted between 1991 and 2003. For each research site, the data include the amount of clinical research dollars spent at the site as well as the name and location of the site and characteristics of the clinical protocol. Data about compounds under development was collected from Pharmaprojects, which contained independent ratings about the relative novelty of compounds under development and the FDA Orange Book, which is a compilation of compounds that have been approved for marketing.

5 The sample comprises data from all of the Top 10 firms, 26 out of the Top 30 firms, and 33 out of the Top 50 firms, where the rankings reflect R&D spending listed in annual reports to shareholders in the year 2000. Companies in the sample spent a total of $41,434 millions in R&D that year. This value corresponds to 82% of the aggregate amount reported by the Top 45 heaviest spenders.
For purposes of the present study, we coded each site for its status as academic or for-profit. Site names were compared with names listed in the American Hospital Association's (AHA) annual survey of acute-care hospitals, as well as to a list of academic medical centers. Sites which were listed in the AHA database as teaching hospitals were coded as academic; all other clinical research sites (save for veterans' hospitals unaffiliated with medical schools and a few non-profit, non-academic hospitals) were coded as non-academic. These included entities such as for-profit hospitals, private practices, and for-profit organizations set up for the express purpose of conducting trials.

We then aggregated the investigator contract information up to two distinct levels of analysis: the clinical trial (i.e., project) level and the geography level. This procedure yielded two samples that we discuss in turn.

4.1.1 Project-level sample

In addition to our dependent variable (the proportion of academic sites in a clinical trial), the data include a number of project characteristics, such as the phase of the trial, the name of the chemical compound being tested, the medical indication for which it is being examined, the length of the trial in weeks, the total number of medical procedures required in the trial protocol, and whether the trial takes place in an outpatient setting. Medical indications were further grouped into fifteen therapeutic classes.

Since we could only reliably ascertain the academic status for U.S.-based clinical sites, the sample was limited to 8,163 trials involving solely U.S. sites; 428
(5.24%) observations consisting of trials beginning in 2002 or beyond were dropped because they involved trials that were likely to be incomplete, yielding a final data set with 7,735 unique clinical trials.

4.1.2 Geography-level sample

Gross revenue and number of contracts for each clinical site was aggregated at the Health Service Area/year-level to create a panel data set of academic and non-academic clinical research volume, measured in number of contracts awarded. Originally, Health Service Areas (HSAs) were defined by the National Center for Health Statistics as a group of contiguous counties which are “relatively self-contained” with respect to their medical care. Their construction provides a level of analysis in which patients generally reside in the same geographic unit as where their health services are rendered, and are conceptually analogous to Metropolitan Statistical Areas.6

To assess the impact of managed care on clinical research, we used available data on the market penetration of Health Maintenance Organizations (HMOs), which are the most prevalent form of managed care, although other names and forms also exist. Panel data on HMO enrollment were generously shared by Laurence Baker and have been analyzed in a variety of papers on the subject of

6We also conducted all the analyses at the county-year level, with substantively similar results. HSAs may be a more meaningful unit of analysis than counties, as they account for situations where individuals living near county borders are inclined to cross those borders to receive medical care. On the other hand, health insurance mandates and legal climates vary from state to state — necessitating the inclusion of state fixed effects in our regression models — so inclusion of a state dummy variable yielded cleaner models for county-level analyses since no counties cross state borders. Specifications in which HSAs were assigned state fixed effects for both states (for example, a St. Louis HSA would include state fixed effects for both Missouri and Illinois), as well as specifications in which data were aggregated to modified HSAs divided by state borders (in which St. Louis would be subdivided into two separate “modified” HSAs) all yielded materially similar results.
managed care (e.g., Baker, 1997, 1999, 2000a, 2000b). The data set includes information on total HMO enrollment and market share for each county in the United States, excluding Alaska.\(^7\) These data were collected by Baker using HMO enrollment information found in the National Directory of HMOs, published by the Group Health Association of America. Additional details on the collection of these data can be found in Baker (1997, Appendix A).

It is important to acknowledge that this measure is at best an imperfect proxy for managed care activity (Baker, 2000a). Unfortunately, when measuring the influence of managed care, applied researchers must trade off breadth of coverage with substantive depth. While cross-sectional surveys provide better measures on the specific cost-containment activities in which insurance plans engage, we rely on the HMO enrollment proxy because it is the only measure available consistently over a length of time matching that of the clinical trial data. Because the HMO data set ends in 1999, the clinical trial level analysis stems from a more restricted set of investigator contracts signed between 1991 and 1999 (vs. 2001 as an end-date in the project-level sample). To evaluate whether the relationship between managed care and clinical trial growth was a function of medical practice size, attributes of clinical sites were searched for through the internet.

Control variables for the panel were collected from a variety of publicly available sources. Total population and demographic variables such as age and

\(^7\)Cities in Virginia were combined with adjoining counties. Parishes in the state of Louisiana and the cities of Baltimore and St. Louis are all treated as counties. Every effort was made to ensure that the panel structure remained constant in light of a very small number of changes in county borders between 1991 and 1999; market share and population information was generally allocated to 1991 geographic boundaries.
ethnicity for each county-year observation were collected from the U.S. Census Bureau. The number of physicians by county, in private practice or in academia, was drawn from the Area Resource File. Average income by county originates from the Bureau of Economic Analysis at the U.S. Department of Commerce. We also implicitly control for density in an area by adding a control for the log of the land mass area is square miles. This is important in so far as the costs of monitoring clinical investigators should imply that pharmaceutical firms have an incentive to locate sites near airports, in areas with high population density. County demographic information was aggregated to the HSA level for those analyses.

The full data set contained 67,401 observations from 1991 to 1999, but only a subset of this data was used for the supply-side analysis. Geographic information was missing from 3,318 observations, and 82 observations from Alaska and Puerto Rico were excluded, as there was no managed care data available for these locations. The remaining 64,001 contracts was further reduced by 5,208 to exclude non-profit, non-academic hospitals. Of the remaining 58,793 sites, approximately half (29,538) were coded as for-profit entities. This population was examined more closely to analyze whether the relation between managed care and clinical trial activity differed among large and small medical practices. Excluded for this ancillary analysis were 2,873 observations that were hospitals, 12,830 observations that were free-standing clinical trial providers, and 425 observations that were staff-model HMOs. 5,407 observations consisted of independent physicians presumed not to be part of a group practice. The remaining 8,005 observations consisted of 1,940 unique entities. Names on this list were searched on the internet to find basic
practice details such as specialty and to determine the number of physicians practicing associated with the entity. The sample was divided into one consisting solely of observations associated with 1,423 large practices (ten physicians or more) versus another consisting solely of 6,582 small practices and 5,407 solo practitioners (less than ten physicians).

Finally, we collected additional data to examine the endogeneity between clinical trial activity and HMO enrollment. Two types of data were collected to support this analysis (detailed in the appendices): First, we collected information regarding the size distribution of firms from the U.S. Census Bureau's annual County Business Patterns file. Second, we collected information about state laws regulating the small-group insurance market that were passed in a number of states in the 1990s. Data regarding these legislative events were collected by Simon (2000); her efforts and those of others are listed in the footnotes and appendices of a few published and working papers (Buchmueller and Liu, 2005; Hing and Jensen, 1999; Simon, 2005).^8

4.1.3 Procedure-level sample

The procedure-level data set consists of pricing data for 1,227 medical procedures conducted at 140 clinical research sites from 1997 to 2004, which was supplied to us by RapidTrials, Inc. Founded in 1996, RapidTrials developed a database consisting of price information for clinical protocols provided by (mostly non-academic) research sites. The data contain detailed price information for a

^8Importantly, Hing and Jensen (1999) also identify state laws affecting small group health insurance which were already in place before 1990, when our panel begins.
sample of medical procedures performed at each research site, as well as for their counterpart in the Medicare fee schedule. Whereas the Fast Track data is collected from clinical trial sponsors (i.e., pharmaceutical companies), the RapidTrials data is collected primarily from research sites. This data source essentially trades off breadth of detail across the pharmaceutical industry for depth of detail within research sites. These data are typically used to help research sites and trial sponsors budget their estimated costs for novel research protocols whose components consist of procedures that have been completed at other research sites for other protocols. The data used for the present analysis consists of 1,227 observations performed at 140 research sites.

We used the data to compare the prices prevailing for the same medical procedures paid by Medicare and clinical trial sponsors. Doing so enables us to ascertain the extent to which reimbursements for clinical research incorporate rents, since managed care and Medicare payment levels track themselves fairly closely, according to industry observers. With one exception, all variables for the procedure-level analysis are comprised of data from the RapidTrials database. The lone variable from outside the data set consisted of a dummy variable for whether the research site is located in an area where HMO penetration exceeds 30%.

Independent variables of interest included indicator variables for a variety of site types, including dedicated clinical research center, private medical practice, or other

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9This corresponds to the 75th percentile of the county-level distribution of HMO penetration in 1999, the last year for which we have data available.
type of site. Additional control variables include whether the procedure requires a subject visit, laboratory visit, sample collection, or health status assessment.

4.2 Descriptive statistics

Descriptive statistics for the project-level sample are displayed on Table 1. As can be seen in Figure 2, the distribution of the fraction of academic investigators ($\%AMC$) in a trial exhibits two mass points at 0 and 1, but 53.30% of the observations fall within the open interval $]0;1[$. Thirty percent of the trials pertain to drugs that had already been approved by the FDA (though not necessarily in the same therapeutic indication). In Figure 3, we take a cursory look at trends regarding the composition of drug project portfolios over time. We examine whether the proportion of trials pertaining to new treatments has markedly increased or decreased over time. We measure novelty in three ways: whether the drug being tested is a novel compound, whether it is already approved, and whether the trial is designed to address an ailment already well-treated by existing drugs. The proportion of trials for novel compounds has increased, but so has the number of trials pertaining to already-approved drugs. The proportion of trials addressing well-treated diseases has remained flat during the same period. In light of this evidence, we can already conclude that it is very unlikely that an increase in the proportion of data-intensive projects could by itself account for the rise of for-profit experimental medicine.

Descriptive statistics for the project-level sample are displayed in Table 2. Figures 4A and 4B display maps of U.S. counties, where each county is shaded in
light or dark tones to indicate the intensity of clinical research activity in the county. It is apparent from these maps that a relatively small number of counties account for the bulk of the activity. To reinforce this point, Figures 5 displays the county-level distribution of the number of clinical trial contracts between 1991 and 2001, broken down by affiliation status. In this analysis, as in the multivariate results below, we exclude any geographic unit in which there is no clinical trial activity during the whole period. The distribution for both these variables is particularly skewed for academic sites, because the number of counties in which a teaching hospital or a medical school exists is a relatively small subset of the counties in which clinical research is conducted. Finally, Figure 6 is a map documenting the growth of HMO enrollment throughout the continental U.S. in the 1990s.

Descriptive statistics for the variables in the procedure-level sample are displayed in Table 3.

4.3 Econometric considerations

4.3.1 Project-level sample

To ascertain whether pharmaceutical firms' reliance on academic investigators is influenced by the importance of knowledge-production activities, relative to data-production activities, we model the determinants of the fraction of academic investigators in a clinical trial, $\%AMC$, using the fractional logit estimator (Papke and Wooldridge, 1996). Briefly, given a sequence of observations $(y_i, X_i)$: $i = 1, 2, \ldots, N$ where $0 \leq y_i \leq 1$ for all $i$, this estimator assumes that the
conditional mean of $y$ given the observables in $X$ takes the form:

$$E[y_i | X_i] = \Lambda(X_i \beta)$$

where $\Lambda(\cdot)$ is the logit c.d.f. This ensures that the predicted values of $y$ lie in the interval $]0; 1[$. Estimation proceeds by Quasi-Maximum Likelihood (QML). The resulting estimate is consistent as long as the conditional mean is correctly specified. Further, an asymptotically-robust variance-covariance matrix is easily produced using readily available software packages.

4.3.2 Geographic-unit level sample

We first examine the determinants of HMO enrollment across and within geographic areas. To do so we regress the log of the number of HMO enrollees on HSA and state characteristics, including variables that capture the friendliness of the legal environment towards managed care insurance plans. Second, we look at the effect of HMO enrollment on various measures of clinical trial activity. The skewed distribution of the dependent variables (the number of clinical sites or the amount of clinical research expenditures in a geographic unit) makes the use of traditional least squares regression techniques problematic. The distribution of these variables exhibits a large mass point at 0 (see Figure 5). As a result, we apply Poisson models to these specifications, which we estimate by quasi-maximum likelihood (pooled cross-sections) or by conditional quasi-maximum likelihood (within geography models). Because the Poisson model is in the linear exponential family, the coefficient estimates remain consistent as long as the mean of the dependent
variable is correctly specified (Gouriéroux et al., 1984). Further, "robust" standard
errors are consistent even if the underlying data generating process is not Poisson.\textsuperscript{10}

Of course, the structure of the health insurance industry and entry into the
clinical research industry could be jointly determined. Both HMOs and physicians
prone to participate in clinical trials might cluster in similar geographic areas
because common, unobserved factors drive entry decisions in both industries. This
endogeneity is of particular concern in the cross-sectional dimension, where one
might suspect that areas in which health care is expensive in ways not accounted for
by our data attract both sets of organizations. In order to identify the causal effect
of HMO enrollment on clinical trial activity, a credibly exogenous source of variation
in HMO enrollment is needed. In the appendix, we document our (unsuccessful)
effort to use variation in state-level regulation of health insurance for small firms to
create exogenous shifters of HMO enrollment. Statistically insignificant second stage
results in an IV framework should not necessarily lead us to not reject the null
hypothesis. However, we stress that our results show a strong association between
for-profit clinical trial activity and managed care penetration. Of course, the
particular pattern of this association suggests that a casual mechanism may be
involved, but our conclusions must remain tempered in light of these disappointing
IV results.

\textsuperscript{10}In fact the PQML estimator can be used for any non-negative dependent variables, whether
integer or continuous (see Santos-Silva and Tenreyro, 2006).
5 Results

5.1 Project-level evidence

We present the results of our analysis of the project-level sample. The
credibility of this analysis hinges on our ability to distinguish empirically between
knowledge-intensive and data-intensive projects. Fortunately, the data set contains
a rich set of characteristics that can plausibly proxy for the relative importance of
knowledge-intensive activities. We begin by measuring the innovativeness of a
project in three distinct ways. FDA Approved indicates whether the drug was
approved for use at the beginning of the clinical trial, according to the FDA Orange
Book. As indicated by the descriptive statistics, nearly 30% of trials involved
compounds that had already been approved by the FDA to be marketed for a
particular indication. These additional trials can represent testing for new
indications, testing for whether specialized populations (e.g., children) can use the
drug, or post-approval testing required by the FDA to address potential safety
issues.

First-in-class corresponds to a novelty rating from Pharmaprojects, a
database which assesses, among other things, the extent to which a chemical
compound is new to the scientific community. For the present paper, we created a
dummy variable coded as one if the drug studied received the highest rating,
indicating that it is the first of its kind. FDA Approved is a dummy variable coded
as one if the clinical trial pertains to a drug already approved in the U.S. (which
might occur if the drug is being tested for new indications or examined on a
specialized population). Finally, *Well-treated* is a dummy coded as one if the drug is being tested to treat a medical condition that is among the ten diseases with the largest number of already approved treatments.\(^\text{11}\)

Further, we add a set of phase dummy variables to the specifications. Drug development is a sequential process beginning with Phase I safety trials, continuing with Phase II “proof of principle” trials, and ending with larger-scale, efficacy Phase III trials designed to validate Phase II results in an environment as similar as possible to that of regular medical practice. Phase IV studies are performed post-approval, often in an effort to ensure acceptance of the new drug by prescribing physicians. Uncertainty regarding the compound’s toxicity, side effects, and other idiosyncrasies is resolved upon completion of each stage, so that one would expect knowledge-production activities to assume decreasing prominence (relative to data-production activities) as development unfolds. There is an important caveat for Phase I trials, which correspond to projects whose degree of complexity vary widely, from the most sophisticated (such as “first-in-man” pharmacokinetic and pharmacodynamic studies) to the most routine and codified (such as bioavailability and bioequivalence studies which can take place at any time along the path to regulatory submission). Unfortunately, the data at hand makes it difficult to disentangle the “routine” from the “complex” Phase I studies. Phase I oncology studies constitute an exception. Because of their harmful side-effects, nearly all cancer drugs are first tested in patients — as opposed to healthy volunteers — so

\(^{11}\)These are otitis media, insomnia, pneumonia, bronchitis, asthma, rheumatoid arthritis, pain, urinary tract infections, skin and soft tissue infections, and hypertension. To select these diseases, we drew from a list of ICD-9 codes and associated drugs provided to us by Frank Lichtenberg.
that one can be fairly sure that these studies correspond to “first-in-man”
experimentations. Our prior is that the proportion of academic investigators
decreases with project phase, with the highest proportion in Phase I oncology trials,
and the lowest in Phase IV trials. We also include three other measures: the length
of the trial in weeks, the total number of medical procedures required in the trial
protocol, and whether the trial takes place in an outpatient setting.

Results from these analyses can be found in Table 4. The various
specifications report QML estimates of the fractional logit estimator, with robust
standard errors clustered by chemical compound. Models (1) through (3) each use a
different metric to assess project innovativeness. The three measures of
innovativeness behave as expected, with more innovative projects being associated
with a higher proportion of academics. Their effects remain statistically significant
in Model (4), in which all three measures are introduced simultaneously in the
specification.

The results pertaining to project phase are more mixed. The proportion of
academics in a trial decreases with project phase, with the notable exception of
Phase IV projects, which are associated with a higher proportion of academics than
Phase III projects. Phase IV trials are performed post-approval, often in an effort to
ensure acceptance of the drug by prescribing physicians. Academics might be better
suited to this credentializing role than are non-academic doctors with limited status
and reputation.

We also find that projects taking place outside of hospital settings, as well as
trials that involve a longer protocol, are associated with a lower proportion of
academic doctors. The number of medical procedures performed bears no apparent relationship with the use of academic or non-academic investigators.

The interpretation of the statistical estimates in Model (4) is subject to caution, since it does not account for the effect of unobserved firm practices related to both observable study characteristics and the choice of investigators. For example, pharmaceutical firms have been shown to exhibit heterogeneity in their "taste for science" in the setting of drug discovery research (Cockburn et al., 2000). Model (5) alleviates this concern by adding to the specification a full set of fixed firm effects. The results are qualitatively similar, although the measure of innovativeness based on FDA approval loses statistical significance in this more demanding specification.12

Overall, the project-level evidence strongly suggests that the availability of investigators with academic and non-academic backgrounds provides pharmaceutical firms with the opportunity to carefully match the composition of the investigator team with the type of problems most likely to arise during the clinical study.

Of course, this conclusion begs the question of why pharmaceutical firms did not engage in such purposeful matching in earlier periods. In addition to demographic changes, we show below that the diffusion of managed care insurance plans, by influencing physicians' incentives, had the unintended consequence of encouraging a large proportion of non-academic doctors to enter the clinical trials industry.

12Indeed, one interviewee emphasized that this measure could be quite noisy. He described several clinical trials he knew of as "cutting edge" that happened to involve new indications for approved compounds.
5.2 The effect of HMO penetration

5.2.1 Evidence from geographic variation

Table 5 presents results pertaining to the core hypothesis of the paper: that the growth of managed care insurance in general, and of HMO enrollment in particular, has contributed to the growth of the “for-profit” clinical trials industry. Conceptually analogous results were found when aggregating to the county as a geographic unit of analysis or aggregating to the Health Service Area (HSA; conceptually analogous to a metropolitan area).

Columns (1) and (2) show that HMO enrollment is more strongly associated with non-academic clinical research than with academic clinical research. At mean levels of the control variables, increasing HMO enrollment from the 50\textsuperscript{th} to the 75\textsuperscript{th} percentile (approximately from 30,500 enrollees to 103,000 enrollees) in a given population size (using the median value of 285,000 people) increases the expected number of non-academic clinical trial contracts in the HSA from 0.89 to 1.16, a 30.81\% increase. The comparable magnitude for academic sites is 7.63\% but the corresponding estimate is not statistically significant. Note that these results control for the size of the physician population in the HSA, both in and out of academia. Therefore, it would be erroneous to ascribe the emergence of for-profit experimental medicine merely to a bottleneck in the supply of academic physicians.

The evidence thus suggests that managed care health insurance created incentives for physicians to substitute “experimental patients” for HMO patients. However, this response did not cut across the medical profession in a uniform
fashion, but was concentrated among the group of investigators facing fewer competing incentives: non-academic physicians. The results in columns (1) and (2) controlled for state fixed effects, meaning that the source of variation in HMO penetration we exploit comes from within states, but between HSAs or counties. We have verified in unreported regressions that these results are also robust to the inclusion of state-specific time trends. Columns (3) and (4) examine whether the results also hold in the within dimension of the data, by estimating conditional Poisson Quasi-Maximum Likelihood models. Unfortunately, there is not enough within-HSA variation in the data to detect a statistically significant effect.

As discussed earlier, there are two, not necessarily mutually exclusive stories, to explain the association between managed care penetration and clinical trial activity across geographic areas. The first story is a purely neoclassical explanation, whereby managed care has increased the returns to physicians to practice in large groups, increasing investment in sunk assets such as IT and diagnostic equipment. The presence of these sunk assets lowers the barriers to entry into clinical research, for they can be redeployed at relatively low cost to support clinical trial operations. The second story, which we favor, is an incentive explanation, whereby the wedge between payments for traditional and experimental care leads physicians to substitute one type of patients for another.

An implication of the first story is that the observed relation between managed care and research activity should be stronger among large medical groups. Columns (5) and (6) of Table 5 examine this possibility, but the results show that the opposite might be true. Although the estimate of the effect is larger in
magnitude for practices of 10 physicians or more, only in the case of the small
practices do we observed a statistically significant effect. This pattern of
correlations casts doubt on the scale rationale as the main driver of the effect of
managed care on research activity across geographic areas.

5.2.2 Evidence from procedure-level data

For the incentive story to hold true, it is necessary that reimbursements for
clinical research incorporate rents, relative to reimbursements for traditional care.
We now present some evidence that clearly point in this direction using
procedure-level evidence. The RapidTrials data set enables us to compare the
prevailing prices for identical procedures when paid for by clinical trial sponsors or
by Medicare.

Several caveats are in order before delving into these data in more detail.
First, contrary to the Fast Track data presented earlier, there is no presumption
here that these procedures stem from a sample of trials that is representative of the
underlying population. The data is collected from clinical sites, with the explicit
goal to allow sponsors to benchmark research payments at the procedure level
against industry norms. As a result, one would expect smaller price variation for the
medical procedures in this sample. Second, the data does not compare the level of
managed care payments with those of sponsor payments. Instead, RapidTrials use
the Medicare fee schedule as a benchmark. Obviously, this is a valid assumption
only in so far as managed care and Medicare levels of reimbursement track one
another closely. Third, it might be hazardous to interpret price variation between
payers for the same procedures as providing *prima facie* evidence of rents. Rather, this wedge could correspond to additional costs that clinical investigators incur when treating experimental patients, such as recording information on a case report form.

With these caveats in mind, we turn to Figures 7 and 8. These figures document the wedge between payments from Medicare and pharmaceutical sponsors in the cross-sectional and longitudinal dimensions of the data, respectively. We find that pharmaceutical firms pay almost three times as much as Medicare for the procedures in the sample on average, although the difference varies enormously across procedures, as well as over time. In particular, there is evidence of a narrowing of the payment gap in the more recent period.

Table 6 presents OLS regression results to further investigate the determinants of the payment gap. All models contain year effects. Column (1) consists of the base model, which incorporates indicator variables for each type of procedure: treatment, radiology, subject visit, laboratory visit, sample collection, or health-status assessment. Columns (2) add independent variables to account for the type of the site in which the procedure data was collected: dedicated research center, private practice, or "other." Column (3) adds an indicator variable for whether the site is located in a county in which HMO penetration is higher than 30% (the 75\textsuperscript{th} percentile of HMO penetration at the county level in 1999, the last year in which data is available). Finally, Column (4) incorporates an interaction effect between site type and the high-HMO penetration dummy. The coefficient for the interaction term between dedicated research center and high HMO penetration
is positive and significant at the 10% level, indicating that the wedge for such centers was particularly high in areas with high HMO penetration.

6 Concluding Remarks

Health policy researchers have long understood that institutional arrangements for the financing and delivery of health care to consumers have important feedback effects on the dynamics of technological change in medicine (Finkelstein, 2007; Azoulay & Tay, 2003; Weisbrod, 1991). In this paper, we provide concrete evidence of such feedback from the perspective of the physician, by highlighting how managed care health insurance has contributed to the rise of the "for-profit" clinical trial industry. We show that geographic areas with high HMO enrollment also see more "for-profit" clinical research activity, but do not see more academic clinical research activity. Our results provide an example of complex feedback, whereby changes in the structure of a downstream industry (medical care) affect the nature of upstream R&D activities (in the pharmaceutical industry).

Of course, the diffusion of managed care health insurance was not the only element of the health care environment that was changing at the time of this study. The 1990s also saw an increase in the cohorts of physicians trained in the age of evidence-based medicine. These physicians might have been more prone to become producers (as opposed to merely consumers) of clinical research data than their elder colleagues, who went to medical school in a period during which randomized controlled trials did not occupy such a prominent place in the curriculum. Moreover, these profit-minded, non-academic physicians might not have been able
to enter the clinical trials industry in the absence of regulatory events, such as the
IND/NDA rewrite of the 1980s. Because of the paucity of data covering the earlier
period, and also because the data at our disposal identifies individual sites (e.g.,
Massachusetts General Hospital, Hill Top Research, etc.), but not individual
physicians at these sites, we can only speculate on the relative importance of these
other contributing factors.
References


### Table 1. Descriptive statistics, project-level data.

<table>
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<tr>
<th></th>
<th>No. Obs</th>
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<th>Std. Dev</th>
<th>Min</th>
<th>Max</th>
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<td>Percent AMC</td>
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### Table 2. Descriptive statistics, HSA-level data.

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<th>Std. Dev</th>
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<th>Max</th>
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<td>HMO enrollees (x1000)</td>
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<td>7,008</td>
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<td>Avg. income (x1000)</td>
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<td>Pop. over 65 (x1000)</td>
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<td>70.362</td>
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<td>Pop. non-white (x1000)</td>
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<td>7,448.7</td>
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<td>942.510</td>
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<td>3.500</td>
<td>22,797</td>
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<td>#MDs, hosp/research</td>
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<td>1,393</td>
</tr>
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<td>#Small Firms (x1000)</td>
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<td>4.245</td>
<td>5.226</td>
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### Table 3. Descriptive statistics, procedure-level data.

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<th>Std. Dev</th>
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<th>Max</th>
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<td>Price differential</td>
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<td>3.418</td>
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<td>Dedicated research center</td>
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<td>Other</td>
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<td>HMO penetration over 30%</td>
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<td>Diagnostic procedures</td>
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Table 4. Determinants of academic/for-profit investigator mix [Fractional Logit Estimator].

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<th>(4)</th>
<th>(5)</th>
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<td>FDA approved drug</td>
<td>-0.138**</td>
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<td>[0.067]</td>
<td>[0.064]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Novel class of drug</td>
<td></td>
<td>0.334**</td>
<td></td>
<td>0.378**</td>
<td>0.259**</td>
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<td></td>
<td></td>
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<td>[0.107]</td>
<td>[0.103]</td>
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<td>Popular ICD9</td>
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<td></td>
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<td>[0.089]</td>
<td>[0.084]</td>
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<td>Phase 1 oncology dummy</td>
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<td>1.127**</td>
<td>1.155**</td>
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<td>1.230**</td>
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<td>[0.203]</td>
<td>[0.200]</td>
<td>[0.202]</td>
<td>[0.196]</td>
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<tr>
<td>Phase 2 dummy</td>
<td>0.990**</td>
<td>1.000**</td>
<td>1.043**</td>
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<td></td>
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<td>[0.088]</td>
<td>[0.088]</td>
<td>[0.084]</td>
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<tr>
<td>Phase 3 dummy</td>
<td>0.583**</td>
<td>0.571**</td>
<td>0.636**</td>
<td>0.636**</td>
<td>0.599**</td>
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<td>[0.091]</td>
<td>[0.091]</td>
<td>[0.086]</td>
</tr>
<tr>
<td>Phase 4 dummy</td>
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<td>0.857**</td>
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<td>[0.122]</td>
<td>[0.121]</td>
<td>[0.118]</td>
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<tr>
<td>ln(No. of procedures)</td>
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<td>0.021</td>
<td>0.028</td>
<td>0.024</td>
<td>0.032</td>
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<td>[0.030]</td>
<td>[0.029]</td>
<td>[0.029]</td>
<td>[0.029]</td>
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<td>Outpatient only</td>
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<td>-0.342**</td>
<td>-0.291**</td>
<td>-0.288**</td>
<td>-0.282**</td>
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<td></td>
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<td>[0.079]</td>
<td>[0.078]</td>
<td>[0.078]</td>
<td>[0.074]</td>
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<tr>
<td>ln(length of trial)</td>
<td>0.105**</td>
<td>0.101**</td>
<td>0.097**</td>
<td>0.098**</td>
<td>0.068**</td>
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<tr>
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<td>[0.020]</td>
<td>[0.020]</td>
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<td>Constant</td>
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<td>0.045</td>
<td>0.198</td>
<td>-0.069</td>
<td>-0.373</td>
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<td>[0.193]</td>
<td>[0.169]</td>
<td>[0.190]</td>
<td>[0.331]</td>
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<td>No</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
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<td>Log Pseudolikelihood</td>
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<td>-4,125.01</td>
<td>-4,111.02</td>
<td>-4,098.14</td>
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<tr>
<td>df</td>
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<td>7,702</td>
<td>7,703</td>
<td>7,700</td>
<td>7,612</td>
</tr>
</tbody>
</table>

Dependent variable in all models represents proportion of sites in a trial conducted in an academic medical center. All models contain 7,735 observations, with standard errors heteroskedasticity robust clustered by unique chemical compound. All models contain fourteen therapeutic class dummies, with oncology being the omitted class, and ten year-dummies, with 1991 being the omitted year. Models with novelty rating include dummy variable (not shown) for “rating unavailable” category. Omitted phase dummy is Phase 1 (non-cancer).

† significant at the 10% level
• significant at the 5% level
** significant at the 1% level
Table 5. Number of Clinical Trial Contracts Awarded Across HSAs [QML Poisson]

<table>
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<th>Model type</th>
<th>(1) Acad. Medical Centers</th>
<th>(2) For Profit</th>
<th>(3) Acad. Medical Centers</th>
<th>(4) For Profit</th>
<th>(5) Medical Groups, 10+ docs</th>
<th>(6) Medical Groups, &lt;10 docs</th>
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<tr>
<td>ln(HMO enrollees)</td>
<td>0.066</td>
<td>0.223</td>
<td>0.041</td>
<td>0.038</td>
<td>0.301</td>
<td>0.157</td>
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<td></td>
<td>[0.052]</td>
<td>[0.077]</td>
<td>[0.026]</td>
<td>[0.027]</td>
<td>[0.286]</td>
<td>[0.066]</td>
</tr>
<tr>
<td>ln(Population)</td>
<td>-2.149</td>
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<td>-3.590</td>
<td>-2.940</td>
<td>-0.916</td>
<td>-0.198</td>
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<td>[0.916]</td>
<td>[1.215]</td>
<td>[1.414]</td>
<td>[2.654]</td>
<td>[3.136]</td>
<td>[1.346]</td>
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<tr>
<td>ln(Avg. income)</td>
<td>0.441</td>
<td>0.720</td>
<td>1.504</td>
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<td>[0.342]</td>
<td>[0.707]</td>
<td>[1.194]</td>
<td>[0.324]</td>
</tr>
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<td>ln(Pop. over 65)</td>
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<td>-0.498</td>
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<td>[0.631]</td>
<td>[0.873]</td>
<td>[1.114]</td>
<td>[0.408]</td>
</tr>
<tr>
<td>ln(Pop. under 15)</td>
<td>1.375*</td>
<td>-0.196</td>
<td>1.774</td>
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<td>[0.812]</td>
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<td>ln(Pop. non-white)</td>
<td>0.142</td>
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<td>-0.401</td>
<td>0.097</td>
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<td>[0.373]</td>
<td>[0.819]</td>
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<tr>
<td>ln(MDs, Office-based)</td>
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<td>0.830</td>
<td>0.164</td>
<td>0.407</td>
<td>1.582</td>
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<td>[0.330]</td>
<td>[0.525]</td>
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<td>-0.269</td>
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<td>[0.106]</td>
<td>[0.100]</td>
<td>[0.231]</td>
<td>[0.090]</td>
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<td>ln(Small Firms)</td>
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<td>-0.763</td>
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<td>[0.322]</td>
<td>[0.629]</td>
<td>[0.902]</td>
<td>[0.839]</td>
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<td>ln(Area in Square Miles)</td>
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<td>0.289†</td>
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<td>0.330</td>
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<td>Log Likelihood</td>
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<td>-6,056</td>
<td>-12,297</td>
<td>-966</td>
<td>-4,053</td>
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</table>

Columns (1), (2), (5), and (6) are pooled cross-sectional models, estimated by QML Poisson. Columns (3) and (4) are estimated by conditional fixed effects quasi-maximum likelihood.

Dependent variable in all models consists of count of sites in a Health Service Area (HSA) that are academic, for-profit (all), and large and small medical practices. All models contain year and state fixed effects. Heteroskedasticity-robust standard errors are in brackets, clustered by Health Service Area.

* significant at the 10% level
† significant at the 5% level
‡ significant at the 1% level
### Table 6. Determinants of Research/Medicare Price Gap [OLS]

<table>
<thead>
<tr>
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<td>HMO Penetr. &gt; 30%</td>
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<td>Dedic. Res. Ctr × %HMO&gt;.30</td>
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<td>[21.431]</td>
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<td>138.439</td>
<td>129.852</td>
<td>140.638</td>
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<td>[24.473]</td>
<td>[26.465]</td>
<td>[26.169]</td>
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</table>

No. of Sites    140  140  140  140  
No. of Obs.     1,227 1,227 1,227 1,227  
Adj. R²         0.235 0.236 0.238 0.240  

Regression type is Ordinary Least Squares. Dependent variable is difference between clinical trials and medicare fee schedule: (Research Price – Medicare Price). Robust t-statistics in brackets. Omitted procedure type dummy is Diagnostic. Year indicator variables are included but not displayed.

* significant at the 10% level
** significant at the 5% level
*** significant at the 1% level
Figure 1. Total number of research contracts for clinical trials, by investigator type.

![Graph showing total number of research contracts for clinical trials, by investigator type. The graph indicates an increase in the number of contracts over time, with a peak in 1996 and a decline by 2001.](image)

Figure 2. Proportion of academic investigators within a clinical trial.

![Graph showing the proportion of academic investigators within clinical trials. The graph displays a decreasing trend in the proportion of academic investigators from 1991 to 2001.](image)
Figure 3. Proportion of clinical trials, by measures of novelty.
Figure 4A. Cumulative number of academic clinical sites, 1991-1999, by county.

Figure 4B. Cumulative number of for-profit clinical sites, 1991-1999, by county.
Figure 5. Distribution of mean annual number of clinical trial contracts by county.

Figure 6. Annual county-level growth in HMO enrollment.
Figure 7. Clinical research reimbursements incorporate rents.

![Graph showing clinical research reimbursements incorporate rents.]

Figure 8. Medicare/clinical research price wedge.

![Graph showing Medicare/clinical research price wedge from 1987 to 2004.]

Appendix I:
“Small-Group” State Insurance Laws

Small-group state insurance mandates passed during the 1990s fall into three basic categories: the introduction of guaranteed renewal/guaranteed issue laws, ratings rules, and pre-existing condition laws. Guaranteed renewal laws require insurance carriers to renew insurance policies to any existing customer (employer), regardless of whether the past incurred medical costs and experience do or do not justify continuance as a customer. Guaranteed issue laws, frequently passed alongside guaranteed renewal laws, require insurers to sell policies to any customer willing to pay the premium. Laws involving ratings rules limit the extent to which insurers can price an insurance product based on the underwritten expected medical expenses the customer will incur. Finally, some states have passed laws which require that medical coverage be provided for certain pre-existing medical conditions, such that expensive medical conditions which would ordinarily raise the price of insurance must be covered under the policy provided, usually after some waiting period.

As Simon (2005) notes, it is difficult to isolate the effect of any single law because such laws tend to be passed in groups. We followed her analytical approach, whereby the effects of laws are essentially aggregated and states are modeled as having achieved “no reform”, “partial reform” and “full reform,” corresponding to a dummy variable value of 0, 1 and 2 respectively. Because the effect of the individual laws are not the substantive interest of the paper, this choice was driven by pragmatic considerations, most importantly the fit of the first stage that results
from different ways of coding and capturing the effect of the laws. Alternative specifications yielded materially similar results.

Some complications that arose when coding the data on these laws should be noted. In general, states that enact one type of regulation tend to enact other types of regulation simultaneously, leading to severe multicollinearity issues when attempting to code the content of legislations with distinct dummy variables. Further, legislation is usually not identical from state to state, and can even be amended within states — for example, according to one source (Blue Cross and Blue Shield Association), the state of Virginia passed distinct laws addressing pre-existing conditions in 1992, 1993, 1996, 1997 and 1998. Further, the year of passage for state laws was not always identical among data sources. To address these problems, we tried to identify the year during which the most significant state legislation on guaranteed issue/renewal, ratings laws or pre-existing conditions affecting the small group was passed by comparing data sources.

In addition to these state-level events, the passage of federal legislation — the Health Insurance Portability and Accountability Act (HIPAA) of 1996, which took effect the following year — complements reform in some states while subsuming existing reforms in other states. The effect of HIPAA in our panel is that we treat all states in which no law had been passed as of 1996 as having achieved partial reform in 1997 and beyond.
Appendix II:
Skewed outcomes and IV estimation

Estimation of Between-County/HSA Models with Endogenous Regressors. Following the notation of Windmeijer (2008), we choose to write our basic model:

\[ y_i = \exp(X_i' \beta + \eta_i) = \mu_i \nu_i \]

The multiplicative error term \( \nu_i = \exp(\eta_i) \) ensures that we treat observable influences (the vector of explanatory variables \( X \)) and unobservable factors \( \eta_i \) in a symmetric fashion. The associated moment conditions are

\[ E[\nu_i - 1|X_i] = E \left[ \frac{y_i - \mu_i}{\mu_i} | X_i \right] = 0. \tag{II.1} \]

where \( \mu_i = \exp(X_i' \beta) \). As Mullahy (1997) shows, if \( X_i \) is correlated with the unobservables in \( \eta_i \) such that \( E[\nu_i - 1|X_i] \neq 0 \), then the method of moments estimator that solves (II.1) is no longer consistent. If there are instruments \( Z \) available then

\[ E[\nu_i - 1|Z_i] = E \left[ \frac{y_i - \mu_i}{\mu_i} | Z_i \right] = 0. \tag{II.2} \]

Denoting \( g_i = Z_i \left( \frac{y_i - \mu_i}{\mu_i} \right) \), the GMM estimator that minimizes

\[ Q_N(\beta) = \left( \frac{1}{N} \sum_{i=1}^{N} g_i \right)' W_N^{-1} \left( \frac{1}{N} \sum_{i=1}^{N} g_i \right) \tag{II.3} \]

is consistent for \( \beta \). The efficient two-step weight matrix \( W_N \) is given by

\[ W_N(\hat{\beta}_1) = \frac{1}{N} \sum_{i=1}^{N} g_i(\hat{\beta}_1) g_i(\hat{\beta}_1)' \tag{II.4} \]
where

$$g_i = Z_i \left( \frac{y_i - \exp(X_i' \hat{\beta}_i)}{\exp(X_i' \hat{\beta}_i)} \right)$$

(II.5)

and \( \hat{\beta}_i \) is an initial consistent estimator. The GMM estimates presented below use the moment conditions in (II.2), where the instrument vector \( Z \) contains exogenous county and state characteristics (population, average income, etc.) and the two excluded instruments mentioned above.

**Estimation of Within-County/HSA Models with Endogenous Regressors.**

A similar approach can be applied to within-county or within-HSA models, in the spirit of the fixed effect Poisson model of Hausman, Hall, and Griliches (1984). Let \( y_{it} \) denote the skewed outcome to be explained for county \( i, i = 1 \ldots N \), at time \( t, t = 1 \ldots T \); and let \( X_{it} \) denote a vector of explanatory variables. An important feature of panel data is the ability to control for time-invariant unobserved heterogeneity through the use of unit fixed effects. In count or exponential models, these effects are generally modeled multiplicatively as

$$y_{it} = \exp(X_{it}' \beta + \eta_i) + \epsilon_{it} = \mu_{it} \nu_i + \epsilon_{it}$$

(II.6)

When the vector \( X \) only comprises strictly exogenous variables, the conditional mean of \( y_{it} \) satisfies

$$E[y_{it}|\nu_i, X_{it}] = E[y_{it}|\nu_i, X_{it1}, \ldots, X_{iT}]$$

(II.7)

For this case, Hausman et al. (1984) use the Poisson conditional maximum likelihood estimator (CMLE), conditioning on \( \sum_{t=1}^{T} y_{it} \), which is a sufficient statistic for \( \eta_i \). However, the Poisson maximum likelihood estimator for \( \beta \) in a model with
unit-specific intercepts does not suffer from the incidental parameter problem, and is therefore consistent and the same as the CMLE estimator [see Windmeijer (2008: v-vi) for a short proof]. The associated first order condition for \( \beta \) is equivalent to a moment estimator in a model where the ratio of within-unit means are used to approximate the fixed unit effects. The moment conditions for this within-group

*mean scaling estimator* are given by

\[
\frac{1}{N} \sum_{i=1}^{N} \sum_{t=1}^{T} X_{it} \left( y_{it} - \mu_{it} \frac{\bar{y}_i}{\bar{\mu}_i} \right)
\] (II.8)

If the vector \( X \) contains one or more endogenous variables, but a vector of valid instruments \( Z \) is available, one can estimate the mean-scaling model by substituting \( Z \) for \( X \) in (II.8):

\[
\frac{1}{N} \sum_{i=1}^{N} \sum_{t=1}^{T} Z_{it} \left( y_{it} - \mu_{it} \frac{\bar{y}_i}{\bar{\mu}_i} \right).
\] (II.9)
Appendix III:

Endogeneity of HMO enrollment

Instrument relevance and instrument validity. Past researchers have long been aware of that managed care penetration might be simultaneously determined with other variables of interest, but efforts to deal with this endogeneity have only been met with limited success. The most popular approach has been to rely on use the size distribution of firms to serve as identifying instruments in two-stage least squares regressions (Baker, 1997; Hadley and Mitchell, 1999; McLaughlin, 1987, 1988). Dranove et al. (1998) show that the number of large firms in a geographic area positively influences managed care penetration. Baker (1997) argues that areas with large firms may be particularly attractive to HMOs since large firms are more likely to offer their employees a menu of health insurance policies that may include HMOs. From the point of view of identification, the validity of such an instrument hinges on whether the source of variation in firm sizes across (or within) geographic areas can really be assumed to be orthogonal to unobserved determinants of the outcome of interest. Hadley and Mitchell (1999) argue that industry and work-force characteristics are unlikely to have a strong, direct impact on physician practice choices, but in light of the well-documented firm size-wage relationship (Oi and Idson, 1999), and in the absence of a model explaining whence differences in firm size originate, we choose not to rely on this identification strategy.

We propose an alternative approach that uses variation in state-level regulation of health insurance for small firms to create exogenous shifters of HMO
enrollment. The 1990s were a period of frequent state and federal legislative events that affected the structure of the insurance industry. Health insurance in the United States is primarily provided through employers. The total medical expenses incurred by patients pooled in smaller groups — i.e., employees of small firms — is less predictable, so small employers tend to pay more for health insurance. Further, because large employers provide more stable risk pools, and because the economies of scale in plan administration can be substantial, insurers prefer large employers as customers. In order to reduce the competitive disadvantage small businesses consequently face in labor markets because of their inability to provide affordable health insurance, many states enacted legislation designed to increase the ability of small groups to provide health coverage for their employees.

While the success of such legislation on the availability of health insurance has been debated (Hing and Jensen, 1999; Jensen and Morrisey, 1999; Simon, 2005), the more relevant question for our analysis is how legislation has affected the use of HMOs in particular. On the one hand, some insurers and policy analysts (e.g., Flynn et al., 1997) have argued that such legislation would decrease coverage because it introduces various mandates that drive up the price of insurance. This would suggest that the passage of these reforms has a negative effect on HMO enrollment, as some employers will drop coverage entirely due to its increased cost. However, the increased overall cost of insurance may instead cause employers to shift from more expensive indemnity, fee-for-service products to cheaper managed care plans, thus increasing HMO enrollment. For instance, Buchmueller and Liu (2005) argue that HMOs represent a potentially important self-selection mechanism
because of the restrictions placed on which providers patients can see and under what conditions they can see them. If employers affected by these laws react by substituting HMO plans for commercial indemnity insurance plans, then HMO market share could increase even as the number of employees covered decreases overall. For our purposes, whether this substitution effect dominates does not really matter, and is a question best answered by the data itself. What does matter is that this effect of the legal environment influence the market for clinical research only through its effect on HMO enrollment. This assumption forms the basis of our identification strategy.

We constructed two instrumental variables: a dummy variable to capture the main effect of the laws on HMO enrollment, and an interaction term between the presence of a law in a state and the number of potentially affected firms in a given locale. These instruments address the endogeneity problem to the extent that the laws are passed by states and are not endogenously driven by the structure of the clinical trials industry. Of course, one might worry about the political economy of the laws, that is, that they may have been passed because of changing economic climates in a state (Besley and Case, 2000). This seems unlikely here, since these laws were enacted because of concerns regarding the downstream pricing and delivery of health care services, not because of concerns regarding upstream health care R&D.

**Results.** We begin by reporting results from a first-stage analysis of the determinants of HMO enrollment between and within counties in Table A1.
Model (1) merely regresses the log of the number of enrollees in a county on standard demographic controls. Model (2) documents a correlation between the number of small firms in a county (the threshold for smallness varies by county in accordance to the state statutes that are introduced in the subsequent models). Model (3) introduces our two excluded instruments. At the mean of the data, we find that states that pass "small group" mandates see a 4.79% increase in HMO enrollment after the enactment of the law, relative to states that did not adopt the mandate. Interestingly, counties with more affected firms in fact have lower HMO enrollment, compared to counties with fewer affected firms. This is consistent with Buchmueller and Liu's (2005) argument that these mandates lead some small firms to drop coverage altogether, while larger firms downgrade their menu of health plans and start offering managed care options when none might have been available before. Model (4) shows that these results do not change substantially in the within-county dimension of the data.

We perform $F$-tests of the hypothesis that these two variables are jointly different from zero, and easily reject the null. To summarize, small group mandates did affect HMO enrollment, and they affected counties differentially depending on their distribution of firm size. Our maintained assumption is that this source of variation in HMO enrollment is orthogonal to unobserved determinants of clinical research activity across geographic areas.

Table A2 presents our second stage GMM estimates. They results are disappointing. The estimates are not statistically significant, and in the case of for-profit research activity, the magnitude is very small and of the "wrong" sign.
Clearly, the instruments described above do not allow us to establish a causal relationship between managed care penetration and the rise of for-profit experimental medicine. Our results could merely constitute an artifact of endogenous locational choice by HMOs and physicians. We remind the reader that the failure to reject the null when using instruments is not necessarily damning for our hypothesis, since IV estimates are less efficient than the Poisson QML estimates presented in Table 5 under the null hypothesis that HMO penetration is exogenous.
Table A1. First stage regression: Determinants of HMO penetration among HSAs

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<th>(2) Cross-Section</th>
<th>(3) Cross-Section</th>
<th>(4) Within</th>
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<td>ln(population)</td>
<td>4.077 (0.947)</td>
<td>5.322 (1.001)</td>
<td>5.015 (1.008)</td>
<td>12.063</td>
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<tr>
<td>ln(avg. income)</td>
<td>1.125 (0.509)</td>
<td>1.856 (0.542)</td>
<td>1.971 (0.543)</td>
<td>-1.872</td>
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<tr>
<td>ln(pop. over 65)</td>
<td>-1.376 (0.287)</td>
<td>-1.201 (0.284)</td>
<td>-1.125 (0.285)</td>
<td>-5.733</td>
</tr>
<tr>
<td>ln(pop. under 15)</td>
<td>-0.809 (0.739)</td>
<td>-1.025 (0.731)</td>
<td>-0.765 (0.733)</td>
<td>-7.374</td>
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<tr>
<td>ln(pop. non-white)</td>
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<td>-0.121 (0.103)</td>
<td>-0.123 (0.103)</td>
<td>-2.474</td>
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<tr>
<td>ln(#MDs, office-based)</td>
<td>-0.382 (0.264)</td>
<td>-0.032 (0.251)</td>
<td>0.007 (0.245)</td>
<td>1.342</td>
</tr>
<tr>
<td>ln(#MDs, hosp/research)</td>
<td>0.034 (0.066)</td>
<td>-0.024 (0.066)</td>
<td>-0.035 (0.065)</td>
<td>-0.096</td>
</tr>
<tr>
<td>ln(area in sq mi)</td>
<td>-0.318 (0.110)</td>
<td>-0.253 (0.109)</td>
<td>-0.254</td>
<td></td>
</tr>
<tr>
<td>ln(#small firms)</td>
<td>-1.548 (0.381)</td>
<td>-1.381 (0.379)</td>
<td>1.208 (1.693)</td>
<td></td>
</tr>
<tr>
<td>Regulated State</td>
<td></td>
<td>1.821 (0.267)</td>
<td>1.540 (0.250)</td>
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</tr>
<tr>
<td>Regulated State × ln(#Small Firms)</td>
<td></td>
<td>-0.229 (0.031)</td>
<td>-0.193 (0.028)</td>
<td></td>
</tr>
<tr>
<td>R²</td>
<td>0.675 (0.679)</td>
<td>0.688 (0.326)</td>
<td>29.385** (25.535)</td>
<td></td>
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</tbody>
</table>

Chi² test: LawVars = 0

Robust standard errors in brackets.

* significant at the 10% level
** significant at the 5% level
*** significant at the 1% level
Table A2. Number of Contracts Awarded across HSAs, GMM Estimation using Law Instruments.

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<td>AMCs</td>
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<td>ln(#HMO enrollees)</td>
<td>0.089</td>
<td>-0.006</td>
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<td>[0.107]</td>
<td>[0.114]</td>
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<tr>
<td>ln(population)</td>
<td>-3.998***</td>
<td>-0.639</td>
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<tr>
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<td>[0.590]</td>
<td>[0.717]</td>
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<tr>
<td>ln(avg. income)</td>
<td>-0.469**</td>
<td>0.625</td>
</tr>
<tr>
<td></td>
<td>[0.177]</td>
<td>[0.178]</td>
</tr>
<tr>
<td>ln(pop. over 65)</td>
<td>0.913**</td>
<td>-0.195</td>
</tr>
<tr>
<td></td>
<td>[0.147]</td>
<td>[0.202]</td>
</tr>
<tr>
<td>ln(pop. under 15)</td>
<td>2.301**</td>
<td>0.847</td>
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<tr>
<td></td>
<td>[0.355]</td>
<td>[0.426]</td>
</tr>
<tr>
<td>ln(pop. non-white)</td>
<td>-0.150**</td>
<td>-0.183**</td>
</tr>
<tr>
<td></td>
<td>[0.061]</td>
<td>[0.050]</td>
</tr>
<tr>
<td>ln(#MDs, office-based)</td>
<td>0.007</td>
<td>0.561</td>
</tr>
<tr>
<td></td>
<td>[0.199]</td>
<td>[0.174]</td>
</tr>
<tr>
<td>ln(#MDs, hosp/research)</td>
<td>1.448**</td>
<td>0.186</td>
</tr>
<tr>
<td></td>
<td>[0.054]</td>
<td>[0.044]</td>
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<tr>
<td>ln(#small firms)</td>
<td>0.667**</td>
<td>0.513</td>
</tr>
<tr>
<td></td>
<td>[0.192]</td>
<td>[0.211]</td>
</tr>
<tr>
<td>ln(area in sq mi)</td>
<td>0.006</td>
<td>0.133</td>
</tr>
<tr>
<td></td>
<td>[0.028]</td>
<td>[0.040]</td>
</tr>
<tr>
<td>No of Observations</td>
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<tr>
<td>No of HSA/modified HSAs</td>
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<td>444</td>
</tr>
<tr>
<td>Test of overidentifying restrictions, df=2</td>
<td>9.883**</td>
<td>0.343</td>
</tr>
</tbody>
</table>

HSAs that cross state boundaries are modified by treating each state's portion of an HSA as a separate geographic unit. Heteroskedasticity-robust standard errors are in brackets, clustered by Health Service Area.

† significant at the 10% level
* significant at the 5% level
** significant at the 1% level
III. Doctors, $$ and Drug Development: A Qualitative View

Abstract

The present paper engages in a qualitative analysis of physician career decisions in the United States over the last several decades. The rise in managed care health insurance programs in the past twenty years has eroded physicians' incomes and made practicing medicine less attractive to them. One course of action that physicians, particularly those outside of academia, have consequently responded with is to conduct pharmaceutical company-sponsored clinical trials. Taken collectively, these trials have led to the rise of a for-profit clinical trials industry. We interview seventy physicians and health care professionals in 1999 and 2007 and find qualitative evidence to support this reasoning.
1 Introduction

Managed care has dramatically altered the nature of health insurance for consumers and practice of medicine for health care providers. The rise in managed care health insurance plans over the past twenty years has affected individual physicians by reducing their professional autonomy, emphasizing financial considerations in healthcare decisions, and eroding their personal incomes (Hadley & Mitchell, 1999, 2002; Weeks & Wallace, 2002). Physicians have consequently sought to generate revenues in a number of ways. In the present paper, we focus on conducting pharmaceutical company-sponsored clinical trials as an often-chosen mechanism. Surveys have found that some 10% to 22% of physicians participate in such trials (Ashar, Miller, Getz, & Powe, 2004; Pham, Devers, May, & Berenson, 2004). While health policy researchers have noted that institutional arrangements for the financing and delivery of health care has affected technological change for the industry as a whole (Baker, 2001; Chernew, Hirth, Sonnad, Ermann, & Fendrick, 1998; Weisbrod, 1991), this paper examines more qualitatively the process through which the rise of managed care has led to the growth of a for-profit clinical trials industry. In a prior chapter, we have examined the relationship between the growth of managed care and the for-profit clinical trials industry primarily through the use of econometric models. The purpose of the present discussion, however, is to use qualitative research methods not only to "color" this finding, but also to speculate on contextual factors associated with physician reactions to managed care. Two
waves of physician interviews, conducted in 1999 and 2007, document how career
decisions made by individual physicians support a causal relationship between the
rise of managed care and the growth of the clinical trials industry.

We find that the growth of clinical trials as an industry and as a compensation source for private physicians has occurred for several reasons. First, managed care has reduced the relative per hour reimbursement associated with traditional patient care, causing physicians to substitute more profitable “experimental” patients for their ordinary patients. Second, because managed care has reduced physicians’ incomes, they have increased the number of hours worked to maintain a desired income level. This increase in hours worked, taken in aggregate, increases the market capacity of physician appointments, which has, in turn, enabled physicians to utilize a portion of their collective time in conducting clinical trials. Third, managed care and broader circumstances have reduced the relative volume of clinical trial activity in the academic sector; as physicians leave academia to enter the private sector, they have continued their research activities (Pham et al., 2004). Additionally, from the perspective of pharmaceutical companies, academia has become a less-preferred locus for clinical trials as more non-academic sites have become available and can complete studies more quickly.

Admittedly, there have been also other contributors to the growth of for-profit clinical trials besides managed care; moreover, aside from entry into clinical trials, there have been other consequences of managed care on physician career decisions. As organizational researchers, the mainstream press, and our interview
subjects have noted, the growth of managed care has been associated with such consequences as an increase in elective cosmetic procedures (Freudenheim, 1996), physician practice size (Casalino, Devers, Lake, Reed, & Stoddard, 2003; Kletke, Emmons, & Gillis, 1996), and physician relocation (Polsky, Kletke, Wozniak, & Escarce, 2000). More broadly, physician responses to these financial pressures can be viewed as entrepreneurialism (Pham et al., 2004). Demand side considerations, namely an increase in clinical trial needs by pharmaceutical manufacturers, have also contributed to growth in the for-profit clinical trials industry, though only in part. Although qualitative research methods cannot directly test the relative importance of these dynamics, qualitative analysis can give greater depth of understanding, increasing validity, and clearer context to hypotheses tested using quantitative methods alone (Miles, 1979).

This paper aims to make contributions in several areas of organizational research. First, we seek to give qualitative support to analyses of the health care industry that are typically more quantitative in nature. Second, the paper aims to contribute to the entrepreneurship literature by describing a situation in which macro-level industry dynamics create individual-level incentives; by contrast, much entrepreneurship research that centers around individual decisions tends to focus on traits of individuals making entrepreneurial decisions rather than the economic circumstances that foster those decisions (Thornton, 1999). Third, the paper contributes to the literature on careers by detailing a set of nuances among preferences for self-employment; in different economic environments, patient care
and clinical trials reflect different levels of desirable employment characteristics such as autonomy (Hundley, 2001; Kolvereid, 1996).

The remainder of this paper proceeds as follows. First, the historical of managed care and clinical trials prior to the 1990s are briefly documented. After discussing the interview method utilized, we describe how physicians reacted to managed care in their own careers and also how and why they ultimately participated in (or, in some cases, ignored) the growth of the clinical trials industry. We then frame how these propositions are to be tested in future research.

2 Historical Context

2.1 Managed care

The term "managed care" refers interchangeably to a set of health insurance products as well as an approach to medical decision-making that has gained wide prevalence in the U.S. healthcare industry since the 1980s (see Glied, 2000, for a review). It describes a variety of mechanisms through which health insurers seek both to control costs and to improve or maintain the quality of medical care for their policyholders. Managed care's distinguishing features are usually some combination of the following: (1) utilization reviews and controls that restrict the autonomy of providers' medical decisions, especially for more expensive medical procedures; (2) selective contracting, whereby payers negotiate prices (often unilaterally) and selectively contract with local healthcare providers;
(3) monetary and non-monetary incentives that steer enrollees towards the selected providers; and (4) the assumption of some financial risk by physicians in the form of capitation contracts, in which physicians are compensated on the basis of the number of patients whose health they supervise with less regard to the frequency with which they are seen. In combination, these features have generally reduced the cost of health insurance for consumers compared to indemnity policies, in which physicians are reimbursed for fees that, for all intents and purposes, were much higher and not subject to the above constraints. The term encompasses and is often used interchangeably with Health Maintenance Organizations (HMOs), and features of managed care have been adopted by publicly funded insurance programs such as Medicare and Medicaid. The market presence of HMOs was largely facilitated by 1973 Congressional passage of the HMO Act, which gave managed care insurers greater access to the employer-based health insurance market.

Under an insurance system centered on indemnity, the primary role of insurance had been to provide financial protections for individual consumers experiencing improbable health outcomes. Under managed care, insurers who covered a substantial portion of a population of patients act as a collective agent for those patients-as-health-consumers, resulting in insurers asserting market power over physicians. Using this market power to reduce costs, contract selectively, limit coverage for medical conditions to a standard of care, and pass on financial risk to physicians, managed care lowered the prevailing prices for health insurance, contributing to its growth as an attractive insurance product.
Enrollment in managed care products began to exceed nominal levels in the 1980s, giving physicians little choice but to accept the terms offered by managed care insurers or risk losing patient volume. By 1995, over 80% of physicians had contracts with at least one managed care organization (Emmons and Simon, 1995), and the vast majority of health consumers were enrolled in some type of plan that falls under the umbrella of managed care. The market penetration of managed care varies widely across geographic areas, with concentration highest in California (Glied, 2000).

Some scholarly research (Baker, 1997, 1999; Glied & Graff Zivin, 2002) has considered the impact of managed care on health expenditures and outcomes across both managed care patients and non-managed care patients. At a more obvious level, managed care products would be expected to influence the costs associated with managed care patients. Its influence on the entirety of patients in a medical practice and in a healthcare marketplace, however, occurs through at least three mechanisms (Baker, 1997). First, managed care creates a more competitive environment overall for the market prices charged for medical procedures. Second, managed care reduces the incentive and available revenue for physicians to invest in higher-cost technologies, affecting a technology's availability—and, therefore, the likelihood physicians will utilize that technology with other patients. Finally, managed care spreads conservative behaviors and practice patterns such that an indemnity or fee-for-service (FFS) patient becomes less likely to receive a more expensive treatment than an equivalent managed care patient, lest the physician be perceived as making a decision based on
expected reimbursement rather than medical need. Indeed, one of our interviewees told us, “Indemnity plans look a lot like managed care now. They have utilization review, concurrent reviews... The doctor will always be caught in the middle with a huge [incentive] conflict.” Consequently, the entry of managed care to the market fundamentally alters the health care environment, even for physicians not directly contracting with managed care insurers.

This line of research has also found that managed care has had less success than expected with reducing medical costs. Such a finding may exist because of the lack of an unaffected control environment, given that costs, incentives and behaviors for treating non-managed care patients have themselves been affected by managed care. One frequently raised possibility, as well, is that physicians induce demand for their services in response to reduced revenues (Reinhardt, 1999). Indeed, reductions in fees for certain procedures have been found to correlate with an increased volume of those specific procedures (Cromwell & Mitchell, 1986; Yip, 1998). The overall usage of medical procedures across a population is similarly inversely correlated with fee reductions (Reinhardt, 1996). Others have found that, when the ambiguity of medical circumstances permits a choice in procedure, physicians affected by managed care have erred toward recommending a more remunerative option (Goodrick & Salancik, 1996; Gruber, Kim, & Mayzlin, 1999).

This body of evidence is consistent with the line of reasoning presented by McGuire and Pauly (1991) who describe how income incentives drive physician behavior. According to this literature, a cut in physicians' income such as that
caused by managed care leads a physician to undertake efforts to restore income to prior levels. While this literature has argued that demand inducement is a commonly used mechanism for generating income, the present research emphasizes that clinical trials also represents a key alternative means for doing so.

2.2 Clinical trials and the development of new pharmaceutical compounds

Clinical trials as an industry essentially arose to address regulatory requirements for the development of new pharmaceutical compounds. In order to gain regulatory approval for market introduction, the United States Food and Drug Administration (FDA) or its foreign equivalents require that a pharmaceutical company provide documented evidence of a drug's effectiveness through adequate and well-controlled clinical investigations. Following the synthesis of a new molecular compound, pharmaceutical companies file an Investigational New Drug (IND) application with the FDA to obtain permission to test the compound's efficacy in treating a particular ailment, known as an "indication". Such efficacy is demonstrated through a series of experiments involving human subjects, in which a physician typically administers a medical treatment through randomized controlled trials. These experiments, more commonly described as clinical trials, can involve dozens of physicians and thousands of patients in order to generate documentation of a compound's effectiveness sufficient to meet FDA requirements.
Traditionally, most clinical trials were conducted by physicians employed in academic medical centers. Pharmaceutical companies' partnerships with academic physicians occurred as early as the 1920s (Swann, 1988). The emergence of the modern medical school with full-time clinical faculty (Fye, 1991; Rothstein, 1987) played a part in what became an established drug development process. Since the early 1990s, however, academic organizations have gradually declined as the primary locus of industry-sponsored drug development activities. Instead, clinical trials have taken place outside academic institutions: in independent hospitals, private practices and for-profit, dedicated clinical research sites. The proportion of academic clinical sites decreased steadily from 70% of U.S. sites in 1991 to 30% by the end of the decade (Hovde & Seskin, 1997; Zisson, 2001).

Some of this shift can be attributed to bifurcation in the drug development process between idea-generation and data-generation (Azoulay, 2004). Fueled by the FDA's need for an increasing amount of data to evaluate a compound's efficacy (Carpenter, 2004), the sheer number of research subjects and quantity of physician investigators requires the conducting of clinical trials at multiple research sites. In order for the data to be comparable across all research sites, research protocols consequently require that experiments be conducted in an identical fashion, leaving little autonomy for physician investigators. In such trials, the relative emphasis is on the generation of data rather than advancement of science. By contrast, some clinical research, particularly early stage research, requires physician investigators to follow their scientific intuition in a process of
discovery. Pharmaceutical companies thus construct their clinical trials to involve some combination of data-generating and knowledge-generating research efforts (Azoulay, 2004). As informed by our qualitative research, the growth in for-profit research has correlated with the growing need for data generating trials in which academic physicians tend to decline participation.

The growth of a for-profit clinical trials industry has been fueled not only by changes in the needs of pharmaceutical companies, but also by the incentives individual physicians face both inside and outside of academic contexts. In the remaining portion of this paper, we discuss how motivations of physicians concerning their willingness and availability to conduct clinical trials have flowed directly out of their working in a managed care environment.

3 Method

We conducted two waves of semi-structured interviews, involving about seventy physicians and other health care professionals, in 1999 and 2007. The 1999 wave focused on about forty individuals based in the Boston, Massachusetts, area while the 2007 wave involved nearly thirty individuals located across the United States. These interviews involved a cross section of physicians with varying experiences in both the managed care and drug development industries. We also interviewed several professionals in the pharmaceutical industry who work closely with physicians but who do not possess medical degrees. Interview subjects were identified through extended personal social networks and snowball sampling, as doing do was a cost-effective
way to identify interviewees willing to discuss sensitive matters such as personal incomes and motivations (Spreen & Zwaagstra, 1994). Interviews were conducted primarily over the telephone in 2007 but in person in 1999. We took extensive notes and generated transcripts from these interviews that we then analyzed to identify major themes.

Interview subjects had a wide range of employment backgrounds. Most had formerly or at the time of the interview worked in academic medicine, where they were first exposed to conducting clinical research. Physicians who had left academic medicine generally did so to establish their own private practices or join existing ones. Some interviewees maintained private practices as a primary means of employment, while others used them to supplement income obtained in separate employment. Several worked full-time in the pharmaceutical industry, either for a pharmaceutical firm, a contract research organization (CRO), or in a free-standing clinical trials provider; several others were employed in a hospital setting in either a medical or administrative capacity. All major medical specialties were represented, with particular emphasis on research-intensive specialties such as oncology.

The reactions of individual physicians to working under managed care, taken in aggregate, are consistent with trends seen at the level of the health care industry. Several major premises were nearly universally agreed-upon by interview subjects. Managed care has adversely affected physicians' incomes and their autonomy in medical decision-making. Physicians accepted managed care as an unavoidable circumstance beyond their control, and a “fact of life” associated
with working in the healthcare industry. Physicians described pursuing alternative ways to generate income, such as working longer hours or changing their medical decision-making, as identified in other research (McGuire et al., 1991; Rizzo & Zeckhauser, 2003), but these pursuits were tempered by frequent denial that career decisions were even nominally motivated by financial considerations. One common reaction to managed care was an increased use of clinical trials to generate income, although some indicated that they conducted clinical research because they enjoyed it and that reduced involvement with managed care was fortuitous.

3.1 Limitations

We acknowledge some limitations of the present approach. The qualitative methodology is not designed to test a hypothesis so much as to document a story and propose nuanced elements for testing a causal relationship elsewhere. Snowball sampling, as a methodology, relies on the assumption that members of extended personal networks of the authors and early interviewees are representative of the population as a whole (Spreen et al., 1994). The approach was selected so that interview material could include subjects such as induced demand, financial status, and personal motivations. The approach does, however, risk the possibility that interviewees referred us to physicians whose viewpoints were similar to their own. Apparent convergence of opinions may, therefore, be an illusory conclusion from homophilic tendencies among interviewees rather than an accurate depiction of the healthcare marketplace. However, as there was no
overlap between the 1999 and 2007 interview subject pools, and given the
convergent views between the two time periods and between non-overlapping
social networks, this risk is mitigated.

The population of interview subjects targeted physicians directly affected
by managed care. Early discussions with physicians that we personally knew
revealed that, because of the revenue effects of managed care, physicians were
motivated to maximize the utilization of their professional time to generate
revenues. We relied on snowball sampling because we utilized the goodwill of
physicians we knew personally to give us interview time; physicians who did not
know us through a social network were substantially less willing to forfeit a
portion of their professional time, let alone the state of their personal incomes or
tendencies to violate certain norms. A personal acquaintance interviewee, when
asked to refer colleagues to be interviewed on the subject of managed care,
emphasized how difficult it would be to find willing interview volunteers: “The
whole fact that we as doctors are trying to squeeze every nickel out makes it
harder for a doctor to be willing to talk to someone for fifteen minutes without
getting paid.”
4 Outcomes

We begin with a discussion of the consequences of managed care, followed by a discussion of physicians' reactions to those consequences and a perspective of how those reactions, in aggregate, yielded industry-level outcomes.

4.1 Managed care consequences

Consistent with how medical professionals have elsewhere portrayed managed care (e.g., Hadley & Mitchell, 1997), interviewed physicians described a prototypically negative experience, citing the consequences of managed care: a decrease in income, a reduction in professional autonomy, and hindered access to the patient population. Physicians affected by managed care described how each of these consequences contributed to their career decisions, and consequently contributed to the growth of the clinical trials industry.

First, physicians stated that managed care had “ratcheted down” their incomes by unilaterally choosing to lower payments for the services performed by health providers. As a 2007 specialist expressed, “[Managed care] reduces costs by paying less money for the same thing.” While insurers’ market position as a major payor for health services had existed previously, the rise of managed care embodied an increased frequency with which insurers leveraged their market power. Medical providers as a collective body were too diffuse to negotiate for higher fees and prevented by law from doing so\(^1\). A 1999 hospital administrator

\(^1\) Note that, by law, physicians are unable to unionize or otherwise bargain collectively with insurers (Choudhry and Brennan, 2001).
noted that a lack of sophistication on the part of medical providers contributed to this situation as well: “The hospital loses money on HMO patients. On the variable costs! The deals were not well negotiated.... It is the revenue side of the balance sheet which is in trouble.”

Second, in an effort to reduce the possibility that physicians would perform medically unnecessary (and therefore, financially imprudent) procedures, managed care insurers established a “standard of care” in which a specific procedures must be utilized for a given medical diagnosis. For uncommon diagnoses, insurers required that physicians provide justification for medical decisions. This process, known as utilization review, was accompanied by an insurer’s threat to withhold payment for those procedures deemed unnecessary. Physicians, formerly accustomed to operating unencumbered by this review process, described it as a “bureaucracy”, a “headache”, and a “loss of control” that bristled at their sense of professional autonomy. As one 2007 psychiatrist described:

[Working with HMOs has] meant a lot of time on the phone with someone who didn’t know the first thing about clinical care. In the end, everything I thought was clinically appropriate was accomplished; my recommended procedures were nearly always approved. But it took up a lot of time and was a major nuisance.

Another echoed this sentiment: “The biggest problem with managed care—and of course the declining reimbursement levels were definitely an issue—was the paperwork and the phone calls and prior authorizations to describe what I felt
Physicians not only perceived utilization review as a major nuisance but also as responsible for generating direct costs. Several noted that they had to hire additional staff members to complete insurance-related paperwork, and that they lost valuable time spent arguing with insurance companies on their patients’ behalf for why a given medical procedure should be paid for by the insurer.

In the academic setting, utilization review adversely impacted scholarly research by reducing the ability of academic physicians to administer non-standard care for scholarly research purposes. This circumstance caused a greater need for outside funding to support research efforts. As one 1999 hospital administrator indicated:

> When it was cost-based reimbursement, you could do little things on the side, nobody would notice. Today, that has changed. It’s fraud if you charge the third party payer with procedures which are not part of the standard of care. We have a compliance staff to take care of that. The sponsors don’t want to pay for something, the third party payers say the same, and we are caught in between. Endless hassle. That’s why we end up with 25% of health care costs being administrative.

A 1999 pulmonologist framed the loss of research capabilities as an unintended consequence of managed care: “Managed care made the clinical enterprise more efficient. As a result, everybody had to work harder and think less. It has made it very difficult for anybody who is a clinician to take any of his/her time to do scholarly work.” This physician also described how changes brought on by
managed care affected the medical enterprise beyond managed care-funded patients: They reduced the frequency with which clinicians in an “inefficient” enterprise had the time and the opportunity to analyze research questions and interact with other researchers.

The third component of managed care, selective contracting, also generated undesired effects for physicians. Selective contracting created adverse financial consequences not only for physicians who obtained a managed care contract but also for those that did not have a contract. Managed care patients were given financial disincentive to obtain services from physicians not on their insurer’s list of contracted providers, known as a network. From the point of view of the medical provider, managed care organizations presented a dilemma: They could accept the contractual terms of working with a managed care organization or they could suffer from reduced patient volume caused by patients being steered away by virtue of the physician’s exclusion from the network.

Academic physicians were only modestly insulated from contracting problems and from the managed care experience as a whole. Whereas private physicians’ personal incomes were a direct function of their patient volume, academic physicians were generally paid on salary by employers who were, in turn, paid by the patient population. The income generated for the university during an academic physician’s clinical hours was used to fund scholarly research. A 2007 former academic physician described these direct effects of managed care: “Managed care has not just squeezed private practitioners; it has also squeezed university settings. Universities’ patient populations are also insured by managed
care to some degree, and the lower reimbursement levels have inclined the institutions to look elsewhere for income." A 1999 pediatric gastroenterologist observed, "Ten years ago, the clinical people were doing one day a week of clinic, and the rest was research. By the time I started my training it was two and a half days a week, and now it is four or five days a week pure patient care. The research is the one thing that can give. So it is what is being cut."

4.2 Reactions to managed care

In both the private and academic sectors, the most commonly mentioned reaction of physicians to the income pressure from managed care was simply to see more patients by extending office hours and/or by reducing the amount of time spent with each patient. Indeed, as a 2007 gastroenterologist stated, "I think that the prevailing practice among doctors is to try to maintain a certain level of income. When reimbursements go down, they try to see more patients. It's about how many patients do you have to see to make the same amount of money." At the market level, however, decisions by individual physicians to service additional patients resulted in an increase in the market's supply of available appointments. While the increased supply of appointments might have alone lowered the prevailing price for health services, its effect on physician incomes became exacerbated because it accompanied a simultaneous decrease in healthcare demand.

This decrease in demand was caused by several managed care-driven processes. First, managed care organizations reduced the utilization of and
therefore the demand for medical services by health consumers through the widespread use of co-pays and co-insurance, ostensibly to reduce the moral hazard associated with insurance itself. As established research has shown, when consumers become more directly responsible for medical costs, they became less inclined to utilize medical services (Newhouse et al., 1981). Second, capitation contracts cause physicians to encourage their patients not to obtain office-based medical care for less serious ailments. As a 2007 interviewee described,

_of course we treat capitated patients differently. A patient who is capitated calls with the sniffles, and we tell him, “Take two of these and call me in the morning.” A patient who is paying out-of-pocket or indemnity? “Come on in!”_

Another 2007 primary care physician stated, “If we get a call from an HMO [capitated] patient? We tell our nurses to tell them: Do not come in. Unless you’re dying. Otherwise, people come in with ‘nothing’ problems, and you can’t afford to treat them.” Third, the stricter protocols delineated by utilization review itself directly reduced the demand for certain medical services; for example, managed care organizations have mandated shorter hospital stays or fewer outpatient visits for certain medical conditions. Payments were often made on the basis of a medical diagnosis, rather than on the service provided; physicians were thus provided with an incentive to administer care with as little time and as few medical appointments as necessary. And, as one 2007 interviewee told us, “Lots of things that used to be done on an inpatient basis are now done on an outpatient basis” because of managed care.
Physicians consequently faced the cycle of working longer hours to make up for the falling prices, which increased the market supply for their services, which lowered prices further, causing them to once again work longer hours just to attempt to pursue a now-more elusive target income. As a 2007 private practitioner stated, "I'm only making half of what I made four years ago.... I'm disappointed that we're not getting more revenues from managed care. I'm busier that I've almost ever been, and I'm making barely half the money."

Faced with increasing hours worked and decreasing pay, physicians' choice of outcomes consisted of receiving lower wages, seeking alternative sources of income, or exiting the profession entirely. Indeed, a 2007 cardiologist stated these options quite starkly: "The restriction on care by HMOs, either by denying care or reducing payment, are incentives for doctors like me to be doing one of three things: getting a salaried job like at a VA [Veterans Affairs] hospital, doing clinical trials, or getting out of the business of medicine." Indeed, in a far more relaxed tone, an interviewee currently employed at a VA hospital discussed how managed care didn't affect her at all: "Managed care has squeezed a lot of doctors out of private practice, because they don't make that much money.... [My colleagues] all try to come work at the VA, where they can get a salary and not worry about being able to support themselves."

A secondary consequence was that medical practices grew in size in an attempt to acquire some negotiating leverage against insurers (Casalino et al., 2003). One 2007 oncologist in his mid-30s indicated that he had sought employment in a large practice (employing over 45 physicians) because "there's
safety in numbers.... When you're in a bigger group you control the market in the area. You have more leverage against the insurers, so managed care can't squeeze you as hard." The increase in average practice size did not guarantee successful protection from managed care's effects; large practices or hospitals were still occasionally excluded from a managed care insurer's contracted network. With physicians still working longer hours, the increased market capacity enabled managed care organizations to maintain contracts selectively with some medical practices and exclude others.

Without sufficient patient volume, excluded physicians and practices sought alternative methods not only to generate income but also to utilize their existing assets. Physicians perceived network exclusion as ephemeral, however, and took steps to survive until they could restore their network access. To address the period of exclusion and the accompanying reduction in patient volume, physicians used clinical trials to support their practices. As one 2007 cardiologist told us,

*We would all vie for contracts from the HMOs. We would get a contract for a block of hundreds or thousands of patients, and take care of them, and then we would lose our contract because the HMO contracted with another practice for less money. The patients were moved around like blocks of cattle - it was terrible for them, and that's a whole other story. But without those contracts, the medical practice is hurting financially. Without those contracts, people would do clinical trials to pay for the lights and because*
there's nothing else to do with your time.... It became a way to stay afloat until you could get a contract from an HMO again.

When asked whether entering clinical trials was a common tactic for replacing lost income, a 2007 oncologist who worked full-time in the pharmaceutical industry replied that becoming a physician investigator might lead to "incremental change" in income because the investment in infrastructure necessary to do clinical trials functions as an entry barrier: "[Clinical trials are] not the most efficient way for a physician to increase his income. It would be far more effective to increase the number of patients your practice is seeing." Given the decreasing marginal benefit and decreasing opportunity to increase patient volume, however, many physicians felt they had no choice but to consider alternative tactics besides increasing patient volume. Clinical trial activity thus grew as a direct function of the penetration of managed care organizations into a given market.

4.3 The growth of the clinical trials industry

Variations in project characteristics from the perspective of the pharmaceutical companies that sponsor clinical trials led them to design trials involving a particular mix of academic and non-academic physician investigators. These two categories of physicians tended to conduct, respectively, knowledge generating and data generating clinical trials (Azoulay, 2004). From the perspective of the physician, data generating trials are a means to generate
revenue, while knowledge generating trials tend to be rewarded with scholarly publications and prestige.

Interviewed physicians in both the private and academic sectors claimed to focus their own efforts on involving themselves in trials that were, in their words, “cutting-edge,” “exciting scientifically,” and “interesting,” i.e., knowledge generating. One 2007 private-sector neurologist told us: “I didn’t start into clinical trials for the financial aspect; I did it for the intellectual curiosity.... While it is true that some of the studies I’ve done have been a boon to the bottom line for my practice, at the time that I got into those studies, I didn’t think they would be financially very important.” This same physician told us he avoided late-stage trials because they are “sort of uninteresting” in spite of the fact that they were revenue-generating.

While a trial’s sponsorship is objectively observable, more subjective judgment would be required to determine whether a given trial’s purpose was for generating data or knowledge. Several academic physicians we interviewed were keenly aware of the differences in the motivation of academic and non-academic physicians in industry-sponsored studies. As one of interviewees stated, “[In academia], the currency is authorship... Currency to someone who is running a factory is just going to be profit.” However, academic medical centers were not immune to the same financial pressures that beset private physicians, and pragmatism dictated a growing acceptance of industry funding to finance other academic missions. One 1999 academic pediatrician explained that “there was an era where industry money was considered second-class. There is now increasing
awareness that industry money is a good way to foster research... [so there is now] a greater willingness to cooperate with industry.” A 1999 chief of medicine at a major hospital center told us, “There are people who do only NIH research and see industry-sponsored research as dirty. They have become a vanishing minority. Ten years ago, they held sway.... [T]hen there are some that have become very prosperous by doing mainly industry research. By and large those people do not have the same academic prestige.”

This growing tolerance of revenue-generating trials was driven by pragmatism, seeing trials as a means to an end. A 1999 academic cardiologist stated: “The money has to come from somewhere, partly to support the salary of people, but also to support the research personnel.” A 1999 neurologist described a prolific colleague as doing “twenty different studies simultaneously. He could not survive with the five of them which are really interesting. As a result, he takes on fifteen more which pay for the support staff.” A 1999 internist remarked, “People are so desperate that they will take anything. People have to do stuff with little scientific value to pay the rents and the electricity.” Nonetheless, the direct benefit of participating in industry sponsored clinical trials was not always clear. As one 1999 oncologist lamented:

*How does one become the senior author on a large clinical trial?* I participate in [some] trials [that] do not contribute to my academic advancement one single bit... If I am a good foot soldier, I will eventually be seen as a good foot soldier by benefactors and the powers making these new drugs, so that when the next project comes along, I may be a co-writer
or I will be given a Phase II... My expertise lies [in] clinical trial design.

**How to turn that into academic advancement is still a mystery to me.** [Emphasis added.]

A 2007 academic cardiologist noted that, “The currency in an academic environment is free time. You get that by doing trials.... Industry trials are a very good source of income that yields some free time. The time you earn on clinical trials is always better than you can get on your own just from practicing.” A 1999 pulmonologist aptly concluded,

*There is no doubt that industry’s support tends to be more generous. The fact that one can have discretionary funds available by doing clinical trials, that allow to pay a salary here or there, is very, very useful to divisions. Industry is in part supporting the academic and clinical enterprise. Industry is coming to replace other sources of research support, in this day and age.*

Part of this cultural change may have stemmed from structural changes made by the academic medical centers themselves. In the 1990s, academic medical centers were facing declining revenues due, in part, to managed care’s downward pressure on medical reimbursements on a national level if not on a local level. Moreover, they noticed the growing trend of industry-sponsored clinical research occurring outside of academia. These medical centers consequently began to establish offices for attracting industry-funded clinical trials. These offices streamlined processes and provided a common infrastructure
for all studies being run in the institution, but also advocated among academic clinicians to convince them to participate in industry-sponsored studies.

Such offices were initially geared toward simply bringing enough revenues to support the hospital’s operation. One 1999 director indicated that, at his institution, the clinical trials office “was created because things were dysfunctional... Before, industry [representatives] were making deals directly with faculty members. It was a sort of an ‘old boys’ network.’ A big plus was that some people got a lot of work doing clinical trials.” Another 1999 director stated that, “Academic hospitals are waking up. In 1990, 80% of trial money was going to academic hospital centers. Now it’s down to 40%. That is why many medical schools are now creating institutional CROs” to attract industry sponsored trials.

Offices of clinical research were also assembled in reaction to anecdotes from industry representatives that academic researchers were too slow. This sentiment was shared by individual physicians both inside and outside the academic enterprise. Such offices, however, were sometimes perceived to still slow down the pace of research that industry representatives felt they could obtain in the private sector. Indeed, one 1999 research physician complained:

[My academic hospital’s clinical trials office (CTO)] has done some very nice things, but it moves extremely slowly. In recent years, the pace of [disease X] research has been so fast that it is not uncommon for a [CTO] trial to be plodding along asking its questions, when the pharmaceutical company-sponsored study will have opened and closed a protocol and
already come to the conclusion.... There are [CTO] trials today looking at several treatment strategies for which we already know the answer.

A 2007 physician employed by a pharmaceutical company was also dismissive of working with academic medical centers because of their slow pace, particularly with regard to approvals by Institutional Review Boards, and because there was a growing supply of "people who have been full time academics in the past, but because of a dissatisfaction with the academic world, have left academia." A 1999 director of clinical trials for an academic hospital told us, "We hear all the time: we are too slow and bureaucratic, we don't accrue as well as the other places, we are not interested in studies, when they can call Dr. Smith and start enrolling patients with one phone call." Private physicians, even for cutting edge research, were capable of completing trials much faster than academic offices.

These offices did not simply exist to generate revenues, but also to promote the idea that clinical trials could be in the institution's best interests and to manage the process in a manner that benefited the institution. A 1999 director noted that, "Right now, we lose money on industry [funding], because individuals do not know how to negotiate (they are naïve doctors), and [they fail to account for] effort not included in the budget.... We want to create a for-profit company that will negotiate better, spread the fixed costs, and generate income to investigators." This sentiment was echoed by a 1999 research administrator who noted that academic involvement in clinical trials occurs "because [research physicians] want to be on the cutting edge.... Through clinical trials, they can get access to some really cool stuff. They would do it for
no money, which is scary for us. They don't think of it in terms of covering costs.”

Facilitating revenue generation accompanied other needs as well, such as the creation of a culture within the academic enterprise where industry sponsorship was acceptable, and the need to protect institutional liability. The associate director of one research office stated in 1999, “The idea of making money off [industry sponsored trials] is infuriating to certain people.... Faculty felt that it ran the risk of letting financial incentives override the academic mission. So we repainted it with academic buzzwords, and the idea is now accepted.” Another 1999 director noted that his office’s role was to protect the institution: “If something goes sour, not only the faculty member but also the institution get a black eye.” Another hospital administrator noted that his organization’s office was established because “the malpractice insurance came up with the policy that if there was not a proper agreement executed with the institution, the insurance would not pay if something went wrong. So we formalized the process of contract execution.”

This pragmatism did generate (or at least accompany) some degree of cynicism toward participation in industry sponsored-clinical trial activity, or at least toward participating in trials done for data generation\(^2\). A 2007 cardiologist stated, “A lot of the times doctors who are doing drug development are doing it

\(^2\) When asked to identify colleagues who have conducted clinical trials as interview subjects for the present study, a 2007 private-practice cardiologist deridingly replied, “Do you want to talk to people who do real research? Or drug development that’s not really true research?” Our response was that we were interested in interviewing both types of physicians.
for the money, and the drug companies that give them those sorts of trials don’t really use the data; they’re just using the trial as a way to build a relationship with the doctor so that they will be more inclined to prescribe the company’s other medications.” A 1999 endocrinologist referred to herself as a “snob against people doing clinical trials.” A 1999 epidemiologist reported, “I am actually wary of drug company money: it does not buy you much in your institution, and does not necessarily produce very good science. This is kind of third-rate funding as these things go.” What even the most cynical physicians were willing to acknowledge, however, was the growth in prominence of revenue-generating clinical trials among their peers.

The ultimate consequence has been that many medical practices became inexorably linked to drug development. Physicians expressed concern over possible the long-term consequences of industry-sponsored trials for the future of health care and health research. This sentiment was repeated by so many physicians, particularly academic ones, who combined their pragmatism with a sense of caution. A 1999 pediatric pulmonologist worried that without academic research there would not be “the kind of environment where people explore and have a chance to fail. Industry does not take chances. But in academia, sometimes you produce more knowledge by failing.” A 1999 pulmonologist noted, “The problem is that industry will confine itself and sponsor clinical trials in areas where they think they will make some money. So there are going to be areas where just as much should be done but they are going to not be fostered by industry.” A 1999 academic oncologist noted, “We would adore it if it was all
independent from industry. Our long term vested interest is in the care of patients. Period. A way to get there is clinical trials." A 1999 immunologist focusing on AIDS research stated, "The cutting edge studies are being done by pharmaceutical companies.... [but] some companies do not necessarily want to get the truth. They have their own agenda. They want to put their drug under the best possible light." In sum, as a 1999 hospital administrator stated,

"Some people use this bias to criticize industry and not deal with it. My own view is that we should deal with anybody who will support something which is likely to be good for the support of patients. You acknowledge the bias of industry from the get-go, but that does not mean that you should not work with them, because something is better than nothing.

At the same time, no interviewed physician stated that the trials they themselves participated in were done expressly for the purpose of generating revenues. They were quick to acknowledge and even identify peers they perceived to be conducting trials for the sake of revenues, but those peers did not, in turn, identify themselves as conducting trials to generate revenues. A 2007 physician employee of a pharmaceutical company described how the physician investigators he worked with—largely non-academic—selectively identified which medications they perceived to be cutting-edge, and sub-contracted data/revenue generating trials to colleagues. One cardiologist stoically described a former academic colleague who left to form a private practice:

"[It's] an extremely large group of about 60 cardiologists in the area.

[Colleague name] worked in the cardiology practice at [academic hospital],"
and then went to private practice and founded this group. The first thing they did was to put together a clinical trials group, and a very profitable one at that…. It's a very profitable business. They do it for the money, no question. Admittedly, it's also used as a recruiting tool; they want to show academic physicians that they can still do “research” in a private setting…. [but] when he set it up, he did it to make money.

4.5 Additional industry dynamics

Conducting clinical trials was only one option among many both for replacing lost income and for avoiding other attributes of managed care that physicians viewed negatively. While the bulk of our interviews discussed the clinical trials as a chosen source of revenue, some other alternative choices for supplementing lost income were mentioned as well. As a 2007 primary care physician explained:

We’ll do anything now to squeeze an extra few dollars in the office. Doctors in this area have added a lot of procedures to their practice. A lot of work that we used to send out to a lab we’ll do ourselves because we need the money. Urinalysis with a dip stick? Ten dollars. A pregnancy test—the same kind that you could do at home? Ten dollars.

This same physician informed us that she obtained employment at a clinic specializing in elective cosmetic procedures, after the private practice in which she was employed shut down due to financial pressures. Cosmetic procedures such as Botox injections are generally paid entirely out-of-pocket by private
individuals without involving medical insurance at all. Other physicians whose practices focused on medical conditions not covered by health insurance, such as elective cosmetic procedures or emporiatics, were also less vulnerable to the pressures of managed care, and many physicians increased their offerings in these areas as a means to generate income (Pham et al., 2004).

Several interviewees noted how managed care essentially brought on the arrival of a new type of medical specialty, the hospitalist (see Wachter & Goldman, 1996), though none of the interviewees particularly mentioned it as a path they had personally chosen. Prior to the 1990s, a primary care physician whose patients were admitted to a hospital for inpatient treatment would visit those patients to monitor their health. With the rise of managed care, many private practice physicians extended the hours spent seeing patients in their own offices. While the opportunity cost associated with traveling to and from a hospital to visit with a small number of patients (in comparison to seeing patients in a physician's private office) may have previously existed, the increased pressure to replace lost income essentially caused physicians to seek out opportunities to outsource the hospital-visiting aspect of their medical practice. Hospitalists played this role: they functioned essentially as primary care physicians operating full-time in the hospital environment or, as Wachter and Goldman (1996) referred to it, “specialists in inpatient medicine.” Interview subjects indicated that occasionally working a shift as a hospitalist could also served as a means for recruiting patients and growing one's own private practice.
Still others described how managed care created incentives which caused them to eliminate specific processes. A 2007 gastroenterologist told us that he stopped doing certain procedures that didn’t pay well: “I hated giving it up, because I think it’s an important part of gastroenterology, but you bend with the times.” In a concrete example of demand inducement, a 2007 nephrologist confessed how he regularly asked patients to come in for medical injections that they could otherwise do themselves, in order to obtain the income associated with performing those injections. A 2007 primary care physician stated, “With an HMO patient, I’m far more likely to prescribe antibiotics over the phone just so they don’t come in.” Several physicians also expressed a reluctance to provide medical care during phone consultations as opposed to office visits, for which a physician would receive remuneration either from the patient or his/her insurer. As one 2007 physician stated, “We spend so much time on the phone with patients, and we don’t get paid for phone consultations, so we try to spend as little time as possible on the phone.” With income already declining, the reluctance to perform non-revenue generating functions such as telephone consultations or traveling to visit a patient (in a hospital or elsewhere) continued to increase. Several physicians, as well, indicated that they felt forced to cease seeing unprofitable patients, particularly in Medicare (see also Pham et al., 2004).

Some physicians were more reflective about the origins of their forays into clinical research. A 2007 psychiatrist, working full-time in the clinical trials industry, described his situation as follows:
I look at managed care today, and I am quite glad that I am on this side of the business and not with a private practice. They’re in pretty bad shape. But I chose to enter the trials business not out of foresight or because I was chased by managed care but instead because I was interested in the research component. While I had a private practice for ten years, I discovered over time that I enjoyed doing clinical trials more than anything else, so, in 1999, I decided to do clinical trials full time. Managed care did not push me into it.

A 2007 neurologist described how, at first, he conducted clinical trials because of an intrinsic interest in conducting trials. “Now, doing clinical trials has become an important contributor to our practice’s revenues. The idea of doing studies now is driven in part by whether I can get them funded. If it would help the bottom line, there’s no question about whether I would do it.” Managed care, for physicians such as these, was not a direct cause of their involvement in clinical trials.

Note that this sense of good fortune at not being directly affected by managed care was not limited to physicians conducting clinical trials. A similar sentiment was expressed by physicians who were salaried employees at other types of organizations too, such as non-academic Veterans Affairs hospitals, which are fully supported by the federal government. Some research has also shown that managed care causes a lower willingness among physicians to establish private practices in the first place (Kletke et al., 1996). One might speculate, as well, that the shrinking revenues among private practices caused a
reduced overall number of employment opportunities, leading physicians to find themselves working outside the private sector not out of an expressed preference for conducting clinical research but instead as a product of labor market forces beyond their control but ultimately caused by managed care. Indeed, several interviewees described their first serious exposure to clinical trials as an ordinary consequence of where they happened to find a job. “Life just took me into industry,” as one 2007 oncologist put it.

Some interplay between academic and private settings occurred as well. The growth of clinical trials in the private setting may have directly resulted from revenue shrinkage in academic settings. As described earlier, one cardiology practice indicated that they used clinical trials as a means to recruit academic-minded physicians to the private practice. A 2007 psychiatrist told us that “funding for research at universities has decreased in the last few years. There are, quite simply, fewer opportunities for academic research. So this decline in funding has caused physicians who are interested in research for research’s sake to get involved outside of the academic context by getting their names into clinical trials.”

Several physicians emphasized that in their particular circumstances, despite the pressures of managed care, clinical research did not necessarily generate revenues. A 1999 cardiologist emphasized that “industry is really a contract to do a certain amount of work at a certain price. If I can do it more efficiently, then I could use the money left-over to do other types of research, to answer other types of questions.” Another 1999 cardiologist indicated that the
"problem [is that you] often do not make money on industry-sponsored trials. They know exactly how much it costs to do these things." These sentiments were echoed in 2007 interviews as well.

Certainly, the notion that clinical trials could provide supplementary income was not universally perceived. It is unclear whether this was because physicians did not prioritize financial incentives or because they lacked sufficient understanding of clinical trials' underlying costs. A 2007 oncologist indicated that clinical trials were done to draw in patients to his large group practice: "Our trials are actually a money loser for the practice, consistently. We have to rely on the fact that it is a service to our patients, and justify it non-monetarily." A 1999 pediatric specialist echoed the same sentiment: "Clinical research is not for income. I am losing money on this thing. I do it because I am interested in it and I want to do more than taking care of patients. It's the 'I have accomplished something' feeling. I would hope than in a few years, both patients and other physicians will benefit from what I have done." However, a 1999 physician running a full-time, successful, dedicated clinical trial center stated:

*Our competition comes... from private doctors who do not know their costs because studies are commingled with their practice.... They are first-time, second-time investigators.... They are ready to take on studies that we would think generate losses. They do not take into account the fact that they may lose a day of practice to go to an investigator meeting.... Then they realize they are losing money, or they get an FDA audit that does not
go so well, and they drop out. The problem is that there is an infinite supply of these doctors.

Interviews with the chief executives of two different CROs in 2007 echoed this same sentiment, as one lamented: “[Physicians] are literally subsidizing the industry” because they are unaware of their cost structures but are desperate to dabble in clinical trials because of managed care pressures.

Indeed, several physicians expressed to us that they had explored clinical trials as a strategic option for their practices, but rejected them because they perceived the investment to be too substantial or cost structure too unfavorable. A 2007 academic psychiatrist with a part-time private practice told us he felt that “the infrastructure necessary for doing a drug trial is pretty substantial…. You need to hire a staff just for recruiting patients and managing the trial, and you really need to have a full time operation…. That’s not something that I wanted to be involved with.” A 2007 gastroenterologist told us:

A few times a drug company has sought me out, and they felt that I had a large practice from which to recruit patients for a trial…. It just takes a lot of time from your staff. They pay you per patient. It’s usually a reasonable payment, but it’s a lot of time and a lot of work…. I don’t want to put my practice through the major change that’s involved in getting into the trials business, [even though] I continue to be disappointed that we’re not getting more revenues from managed care.

A 2007 oncologist argued:
A physician can't really just stick a toe in the water in order to get a few extra bucks on the side. It just doesn't happen like that. Because, in order to do a drug study, you need a clinical coordinator, case report forms, you need to spend a lot of time with patients on informed consent, and the procedures themselves. All of that takes time and effort.

Nonetheless, the overall success generated among non-academic clinical trial-conducting physicians did not go unnoticed, neither among private physicians nor academic physicians or even academic administrators. A 2007 psychiatrist who conducted trials on a full-time basis said, “I very frequently get inquiries from other psychiatrists about how to get in the business. They see it as very lucrative, they're tired of fending off managed care, and they think it represents a big business opportunity.”

5 Concluding Remarks

The rise of managed care over the past several decades has yielded many consequences for both health consumer behavior as well as for the practice of medicine, ranging from decreasing health expenditures to establishing standards of care. Scholars have observed that revenue and cost pressures have fostered a growing level of physician entrepreneurialism (Pham et al., 2004). The present paper emphasizes that such entrepreneurialism should be viewed not only from the perspective of the individual physician but also in view of its contribution to the growth of for-profit clinical trials as an industry unto itself.
Lesser understood, however, has been managed care’s more distal impact on drug development as a separate industry. Not accounting for these inter-industry dynamics may have caused scholars to make more restrictive interpretations of managed care consequences such as income effects (Reinhardt, 1996). More specifically, proponents of the target income hypothesis have held that physicians induce demand for their services in order to achieve a target income. If one distinguishes between demand inducement as one in which “the physician either raises fees (where possible) or recommends added services to patients, or does both, whenever his or her income is subjected to downward pressure.” (Reinhardt, 1996: p. 277) then the availability of a substitute source of income from clinical trials supports the notion that income seeking behavior can occur without requiring that induced demand accompany it. The mechanism commonly used to explain the empirical finding where physicians’ efforts to increase their overall income results from an increase in managed care penetration (Rizzo & Blumenthal, 1996) is viewed as resulting from a specific behavior among its conventional patients: “If the cut in fees triggers a noticeable increase in the volume of services rendered by the physician, then most probably that increase reflects the physician’s attempt to push volume beyond the increase triggered by [patient] demand” (Reinhardt, 1996: p. 280).

The significance and existence of induced demand has been debated in the economics literature, and accompanies discussions concerning the morality of physician behaviors. On the one hand, econometric evidence supports the notion that economic agents seek to increase income where feasible, and that physicians
are susceptible to the same economic incentives and behavioral tendencies. On the other hand, physicians are more traditionally viewed as responding to a demand for their services rather than creating it (Reinhardt, 1996). The occasional situation where a decrease in fee schedules accompanies an increase in utilization can extrapolate to an assumption that induced demand might be the sole mechanism for fully or partially replacing lost income. In this view, differences between a reduction in fees and a proportional reduction in income become attributed to induced demand. The present paper highlights a more palatable alternative: reducing physician fees causes physicians to replace lost income by generating new revenue from a source other than health consumers.

The present paper also aims to contribute to the literature on entrepreneurship. The arrival of clinical trials as a for-profit industry beckons closer examination of the underlying activity of the individual enterprises that aggregate up to the industry level. A sociological view of entrepreneurship (Thornton, 1999) classically views organizational founding either from the perspective of examining the entrepreneurial opportunities available, defined as the demand side, or the perspective of examining the individuals who pursue those entrepreneurial roles, defined as the supply side. The demand side view has commonly described entrepreneurship as resulting from objective opportunities created by market structures and ecological niches. The supply side view, conversely, has typically examined psychological traits and cultural influences that cause individuals to establish new businesses. Thornton (1999) notes, however, that supply-side research has focused too extensively on individual
traits and not enough on the structural influences that foster entrepreneurial behavior, independent of the demands that market structures generate (see also Martinelli, 1994). The present paper provides a concrete example of a situation where market structures affect the incentives and motivations of individuals to become more inclined to pursue entrepreneurial activity: To the clinical trial industry, managed care is an exogenous change that happens to affect that industry and foster participation in it. The inclination for individual physicians to conduct clinical trials as a new source of revenue is not viewed as a function of personal characteristics but instead as a consequence of macro-level changes in the health care market structure in which they are embedded.

Future research efforts can continue to examine the focal hypotheses on a quantitative basis. While we test the relationship between managed care and clinical trials growth elsewhere, the qualitative research emphasizes the importance of particular control variables. These include such factors as the availability of salaried employment alternatives (i.e., hospitals) and the presence of an affluent population as a proxy for the demand for elective cosmetic procedures. Certainly the role of demand for clinical trial providers by pharmaceutical companies plays a role as well; as the supply of clinical trial providers increases, the compensation available through that mechanism would be expected to decrease in return, once demand stabilizes. In the long run, as managed care has become a stable element of health care rather than a changing component, and as key attributes of managed care permeate throughout the
health care system, one would expect the downstream effect of the supply of clinical trial providers to stabilize as well.
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