Doctors, $$ and Drug Development: The Rise of For-Profit Experimental Medicine

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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.

Keywords: managed care, clinical trials, drug development, induced demand.

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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 re-

search 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.

We also conduct interviews of two separate groups of physicians, both in 1999 and in 2007. These physicians had varying degrees of exposure to managed care, clinical trials, and academic medicine, and represented a broad spectrum of career backgrounds and medical specialties. We use the qualitative evidence to provide anecdotal support for our hypotheses, and to probe in more detail than the econometric evidence would permit the origins and likely evolution of the for profit clinical trials industry.

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. Sections 5 and 6 respectively present the main qualitative and econometric results, while Section 7 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 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).

[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).

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 in-

vestigations, 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 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 regard-

[2]See Glied (2000) for a review.

ing 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 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).[4] 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

[3]Some 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, 1992; Reinhardt, 1996; 1999).

[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. Freudenheim (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.

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 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.[5] 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.

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

[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.

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 geo-

graphic 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 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-

[6]We 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.

[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.

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 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 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.

[8]Importantly, Hing and Jensen (1999) also identify state laws affecting small group health insurance which were already in place before 1990, when our panel begins.

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%.[9] Independent variables of interest included indicator variables for a variety of site types, including dedicated clinical research center, private medical practice, or other type of site. Additional control variables include whether the procedure requires a subject visit, laboratory visit, sample collection, or health status assessment.

4.1.4 Qualitative data

The qualitative data consists of two rounds 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 Boston, Massachusetts while the 2007 wave involved about thirty individuals located across the United States. These interviews involved a cross section of physicians with varying experiences in and exposure to the managed care and drug development industries. Interview subjects were identified through snowball sampling. 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 determine 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 private practices or join existing ones. Some interviewees maintained private practices as a primary means of employment, while others used them to supplement income

[9] This corresponds to the 75^{th} percentile of the county-level distribution of HMO penetration in 1999, the last year for which we have data available.

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. All major medical specialties were represented.

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 $(y_i, X_i) : i = 1, 2, \cdot, N$ 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 $\Lambda(.)$ 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.[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.

[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 Qualitative findings

Several premises were nearly universally agreed-upon by our 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. In response to the reduction in income brought on by managed care, physicians considered several alternatives, such as working longer hours and performing a greater volume of ancillary services. Central to our core argument, one commonly mentioned reaction to managed care was an increased use of clinical research to replace lost incomes. However, many physicians who conducted clinical research indicated that they conducted clinical trials because they enjoyed the work itself, and that reduced involvement with managed care was a fortuitous outcome.

The major changes brought on by managed care each contributed to physicians' inclinations to conduct clinical trials. At the industry level, as discussed earlier, these changes consisted of selective contracting, financial incentives to use particular physicians, utilization review, and capitation contracts. From the perspective of the physician, however, the growth of managed care lowered their overall earnings, reduced their patient volume, and, through utilization review, decreased their sense of professional autonomy.

Physicians' most commonly mentioned reaction to the income pressure from managed care was simply to try to see more patients. Common practices included extending office hours and reducing the amount of time spent with each patient. When we asked whether entering clinical trials was a common tactic for replacing lost income, an oncologist replied that becoming a clinical investigator would only lead to "incremental change" in income, because he perceived the infrastructure needed to do clinical research as a significant entry barrier: *"[Clinical trials are] not the most efficient way for a physician to increase one's income. It would be far more effective to increase the number of patients your practice is seeing."* Explicit mention of demand inducement was rare, likely because of its problematic

ethical undertones. In a single instance, a nephrologist complained that managed care had "forced" him to require patients to come to his office to have a nurse administer a particular injection procedure because in-office administration was reimbursed by insurers while patient self-administered injections left the physician unpaid.

Physicians attempted to increase the number of patients when wages were cut in order to maintain desired income levels. As a gastroenterologist told us:

> *"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."*

Aside from causing an overall decline in income, the selective contracting component of managed care also contributed to the growth of clinical trials. Physicians who did not receive or accept a managed care contract experienced reduced patient volume because patients' financial incentives steered them toward physicians with managed care contracts. Without sufficient patient volume, excluded physicians and practices sought out clinical trials not only to generate income but also to utilize their existing specialized assets, such as office space, equipment, and support staff. Network exclusion, and the accompanying reduced patient volume, was temporary. Clinical trials became not only a means to generate income but also a way to bide one's time. As one cardiologist told us:

> *"We would all vie for contracts from the HMOs. We would get a contract for a bloc 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 flocks 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."*

Conducting clinical trials was certainly not the only response to managed care's growth. Some physicians simply resigned themselves to earning less while others generated income by doing work previously outsourced to laboratories or by performing elective cosmetic procedures. Many physicians (particularly academic ones) emphasized that their own forays into clinical trials were fortuitous rather than intentional:

"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 [i.e., private practioners] are 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."

Several physicians expressed in the qualitative interviews that they had explored clinical trials as an option for their practices and rejected them because they perceived the investment to be too substantial or cost structure too unfavorable. A gastroenterologist told us:

"[The reimbursement for clinical trials] is 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."

This sentiment was echoed by an oncologist working full time in the clinical trials industry, who told us:

"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."

Clinical investigators in private practice sometimes perceived involvement in clinical trials as a source of spillovers on to the traditional part of their practice. One oncologist noted that that clinical trials were a money-loser for his practice. He stated:

"We have to rely on the fact that it is a service to our patients... These people are not going to an academic center for something truly experimental. [They come to us for] something that has some literature behind it to support the likelihood of its success."

Another specialist indicated that he believed the motivation for private physicians to participate in clinical trials comes from *"the idea of being relevant, knowing the latest therapies and drugs, and the idea of enhancing one's own reputation and the reputation of one's practice, i.e., 'So and so does drug studies, so he's on the cutting edge.' "*

An important question to consider is that of the identities of physicians involved in clinical trials — whether they were current or former academic physicians shifting their research

operations into the private sector, or physicians in private practice supplementing traditional care with a new revenue source. We encountered both types of investigators in our qualitative research. The emergence of for-profit experimental medicine has not coincided with a net decrease in the volume of academic clinical research, as can be seen in Figure 1. Many of the interviewed private physicians described their original exposure to clinical trials as coming from their training in an academic setting. However, the growth of managed care may have been the source of some degree of reallocation of physicians from academia to the private sector. As one former academic psychiatrist told us:

> *"[There are people like me] who have been full time academics in the past, but because of a dissatisfaction with the academic world, have left academia. They still have a love of research, and therefore decide to go to a full time research setting... 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 also inclined the institutions to look elsewhere for income... Clinical 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 clinical 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."*

Overall, the prevailing sentiment was one of resignation toward managed care and, aside from exiting the profession, a belief that clinical trials were one means for physicians to shelter themselves from managed care's impact. As a psychiatrist who conducted trials on a full-time basis told us:

> *"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."*

For academic physicians, industry-sponsored clinical trials implied an additional layer of incentive conflicts. The degree of potential participation varied from serving as one investigator enrolling patients for a study among many, to writing the clinical protocol for the study. An oncologist noted:

> *"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."*

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 our interviewees volunteered, *"[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. An academic 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."* A 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."* These examples all reflected a willingness by some academic physicians to participate in clinical trials in any capacity.

Academic medical centers engaged in a variety of activities to stem the exodus of industry-funded clinical research away from their institutions. In the mid-1990s, academic institutions had begun to establish offices for the purpose of 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. These efforts were far from completely effective. A director of clinical trials for an academic hospital lamented:

> *"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 [a proverbial] Dr. Smith and start enrolling patients with one phone call."*

Several academic physicians noted how financial pressures had changed the desirability of attracting industry studies to their institution. One noted, *"There was an era where industry money was considered second-class... There is now a greater willingness to cooperate with industry."* A pulmonologist noted:

> *"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."*

Stigma played a large role in muting the incentives to participate in industry-sponsored studies. The same 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."*

Similar sentiments were echoed numerous times by different academic physicians, whose views of industry studies ranged from indifferent to cynical, or even hostile. One stated *"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."* Another observed:

> *"There are people who do only NIH research, and see industry-sponsored research as dirty... and then 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."*

Fellow academics sometimes viewed investigators with ties to industry as being "tainted" by a conflict of interest. This perspective became increasingly true in light of several scandals involving human subjects protection (Baird, Downie, and Thompson, 2002; Stelfox, Chua, O'Rourke, and Detsky, 1998).

5.2 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.[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

[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.

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 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.

5.3 The effect of HMO penetration

5.3.1 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^{th} to the 75^{th} percentile (approximately

[12]Indeed, one interviewee emphasized to us 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.

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.

5.3.2 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^{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.

It is worth noting that several of our interviewees expressed skepticism that a premium existed at all. Two physician indicated that clinical trials were a money-loser for their practices, and several other interviewees indicated that clinical trials were only a minor, rather than a major, supplemental source of income for their medical practices. A CRO executive told us in 1999 that

> *"[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... ready to take on studies that we would think generate losses.... 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."*

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.

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Table 1. Descriptive statistics, project-level data.

	No. Obs	Mean	Std. Dev	Min	Max
Percent AMC	7,735	0.420	0.377	0	1
FDA approved	7,735	0.292	0.455	0	1
First in class	3,216	0.692	0.462	0	1
Well-treated disease	7,735	0.127	0.333	0	1
Phase 1 (oncology)	7,735	0.041	0.197	0	1
Phase 1 (other)	7,735	0.312	0.463	0	1
Phase 2	7,735	0.220	0.415	0	1
Phase 3	7,735	0.358	0.479	0	1
Phase 4	7,735	0.069	0.254	0	1
No. of procedures	7,735	77.602	66.358	1	909
Out-patient	7,735	0.615	0.487	0	1
Trial length (wks)	7,735	20.586	33.579	0.14	520

Table 2. Descriptive statistics, HSA-level data.

	No. Obs	Mean	Std. Dev	Min	Max
Academic sites	3,789	7.720	20.903	0	177
For profit sites	3,789	7.952	18.813	0	250
HMO enrollees (x1000)	3,789	124.704	346.066	0	7,008
Population (x1000)	3,789	560.721	914.233	21.2	12,091
Avg. income (x1000)	3,789	21.050	5.551	7.972	69.633
Pop. over 65 (x1000)	3,789	70.362	107.659	2.9	1,248.1
Pop. under 15 (x1000)	3,789	121.784	202.365	4.184	2,739.1
Pop. non-white (x1000)	3,789	154.330	438.571	0.159	7,448.7
#MDs, office-based	3,789	942.510	1,827.572	3.500	22,797
#MDs, hosp/research	3,789	52.576	143.857	0	1,393
#Small Firms (x1000)	3,789	8.487	15.380	0.192	120.174
Area in Square Miles	3,789	4.245	5.226	0.070	52.634

Table 3. Descriptive statistics, procedure-level data.

	No. Obs	Mean	Std. Dev	Min	Max
Price differential	1,227	2.722	3.418	-0.854	45.731
Dedicated research center	1,227	0.118	0.323	0	1
Private practice	1,227	0.800	0.400	0	1
Other	1,227	0.025	0.157	0	1
HMO penetration over 30%	1,227	0.316	0.465	0	1
Diagnostic procedures	1,227	0.268	0.443	0	1
Treatment procedures	1,227	0.045	0.207	0	1
Radiology	1,227	0.134	0.341	0	1
Subject visit	1,227	0.422	0.494	0	1
Lab. Test	1,227	0.098	0.297	0	1
Sample collection	1,227	0.028	0.164	0	1
Health status assessment	1,227	0.008	0.090	0	1

Table 4. Determinants of academic/for-profit investigator mix [Fractional Logit Estimator].

	(1)	(2)	(3)	(4)	(5)
FDA approved drug	-0.138*			-0.152*	-0.089
	[0.068]			[0.067]	[0.064]
Novel class of drug		0.334**		0.378**	0.259*
		[0.109]		[0.107]	[0.103]
Popular ICD9			-0.588**	-0.617**	-0.655**
			[0.089]	[0.089]	[0.084]
Phase 1 oncology dummy	1.082**	1.127**	1.155**	1.162**	1.230**
	[0.200]	[0.203]	[0.200]	[0.202]	[0.196]
Phase 2 dummy	0.990**	1.000**	1.043**	1.020**	0.952**
	[0.089]	[0.089]	[0.088]	[0.088]	[0.084]
Phase 3 dummy	0.583**	0.571**	0.636**	0.636**	0.599**
	[0.091]	[0.092]	[0.091]	[0.091]	[0.086]
Phase 4 dummy	0.777**	0.717**	0.793**	0.857**	0.800**
	[0.122]	[0.123]	[0.122]	[0.121]	[0.118]
ln(No. of procedures)	0.014	0.021	0.028	0.024	0.032
	[0.030]	[0.030]	[0.029]	[0.029]	[0.029]
Outpatient only	-0.343**	-0.342**	-0.291**	-0.288**	-0.282**
	[0.078]	[0.079]	[0.078]	[0.078]	[0.074]
ln(length of trial)	0.105**	0.101**	0.097**	0.098**	0.068**
	[0.020]	[0.020]	[0.020]	[0.020]	[0.020]
Constant	0.329†	0.045	0.198	-0.069	-0.373
	[0.172]	[0.193]	[0.169]	[0.190]	[0.331]
Firm fixed effects	No	No	No	No	Yes
Log Pseudolikelihood	-4,129.86	-4,125.01	-4,111.02	-4,098.14	-3,963.91
df	7,703	7,702	7,703	7,700	7,612

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]

	(1)	(2)	(3)	(4)	(5)	(6)
	Acad. Medical Centers	For Profit	Acad. Medical Centers	For Profit	Medical Groups, 10+ docs	Medical Groups, <10 docs
Model type	Cross-Section	Cross-Section	Within	Within	Cross-Section	Cross-Section
ln(HMO enrollees)	0.066	0.223**	0.041	0.038	0.391	0.157*
	[0.052]	[0.077]	[0.026]	[0.027]	[0.286]	[0.066]
ln(Population)	-2.149*	0.191	-3.590*	-2.940	-0.916	-0.198
	[0.916]	[1.215]	[1.414]	[2.654]	[3.136]	[1.346]
ln(Avg. income)	0.441	0.720*	1.504**	2.007**	1.749	0.477
	[0.277]	[0.329]	[0.342]	[0.707]	[1.194]	[0.324]
ln(Pop. over 65)	0.625*	-0.338	1.252*	-0.498	-1.579	-0.061
	[0.313]	[0.369]	[0.631]	[0.873]	[1.114]	[0.408]
ln(Pop. under 15)	1.375*	-0.196	1.774*	2.409*	1.301	0.228
	[0.635]	[0.899]	[0.812]	[1.173]	[2.075]	[0.937]
ln(Pop. non-white)	0.142	0.012	-0.296	0.679	-0.401	0.097
	[0.122]	[0.115]	[0.373]	[0.819]	[0.300]	[0.117]
ln(MDs, Office-based)	0.304	0.830*	0.164	0.407	1.582	0.675†
	[0.406]	[0.385]	[0.330]	[0.525]	[1.198]	[0.396]
ln(MDs, hosp/research)	1.294**	0.092	0.285**	-0.140	-0.269	0.124
	[0.100]	[0.106]	[0.106]	[0.100]	[0.231]	[0.090]
ln(Small Firms)	-0.495†	0.135	-0.424	-0.763	0.736	-0.054
	[0.272]	[0.322]	[0.629]	[0.902]	[0.839]	[0.403]
ln(Area in Square Miles)	0.093	0.289**			0.330	0.232*
	[0.066]	[0.102]			[0.240]	[0.094]
No of Observations	3,789	3,789	1,602	3,717	3,789	3,789
No of HSAs	421	421	178	413	421	421
Log Likelihood	-3,057	-5,719	-6,056	-12,297	-966	-4,053

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]

	(1)	(2)	(3)	(4)
Dedicated Research Center		31.825	31.451	1.521
		[26.305]	[26.193]	[30.458]
Private Practice		21.205	21.643	12.466
		[15.718]	[16.938]	[20.293]
Other Site Types		30.506	35.000	29.999
		[29.844]	[32.127]	[29.774]
HMO Penetr. > 30%			15.435	-18.488
			[13.886]	[16.563]
Dedic. Res. Ctr × %HMO>.30				89.709†
				[45.772]
Private Practice × %HMO>.30				28.686
				[22.485]
Treatment Proced.	-149.849**	-148.666**	-150.767**	-148.303**
	[21.152]	[21.346]	[21.431]	[20.965]
Radiology	-55.310†	-54.670†	-54.884†	-53.156†
	[29.176]	[29.143]	[29.279]	[29.038]
Subject Visit	-172.959**	-172.465**	-172.236**	-170.621**
	[20.076]	[20.098]	[19.993]	[19.816]
Lab. Test	-187.447**	-185.453**	-185.407**	-181.312**
	[22.797]	[22.717]	[22.606]	[21.824]
Sample Collection	-195.558**	-193.574**	-193.393**	-190.696**
	[25.447]	[24.922]	[24.928]	[24.353]
Health Status Assessment	-215.844**	-215.902**	-218.795**	-219.794**
	[23.097]	[23.316]	[24.852]	[25.718]
Constant	160.080**	138.439**	129.852**	140.638**
	[21.093]	[24.473]	[26.465]	[26.169]
No. of Sites	140	140	140	140
No. of Obs.	1,227	1,227	1,227	1,227
Adj. R^2	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.

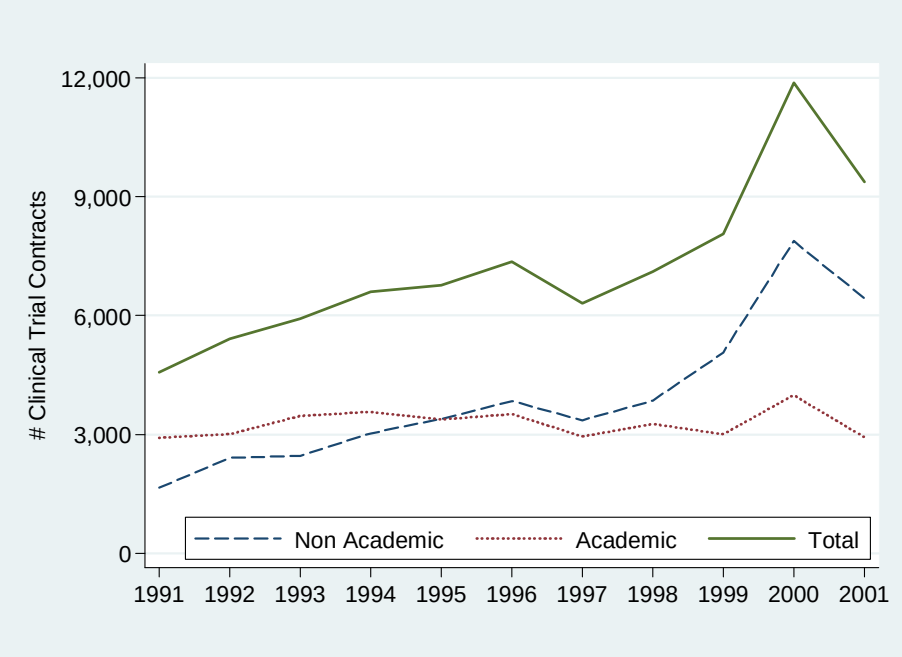


Figure 2. Proportion of academic investigators within a clinical trial.

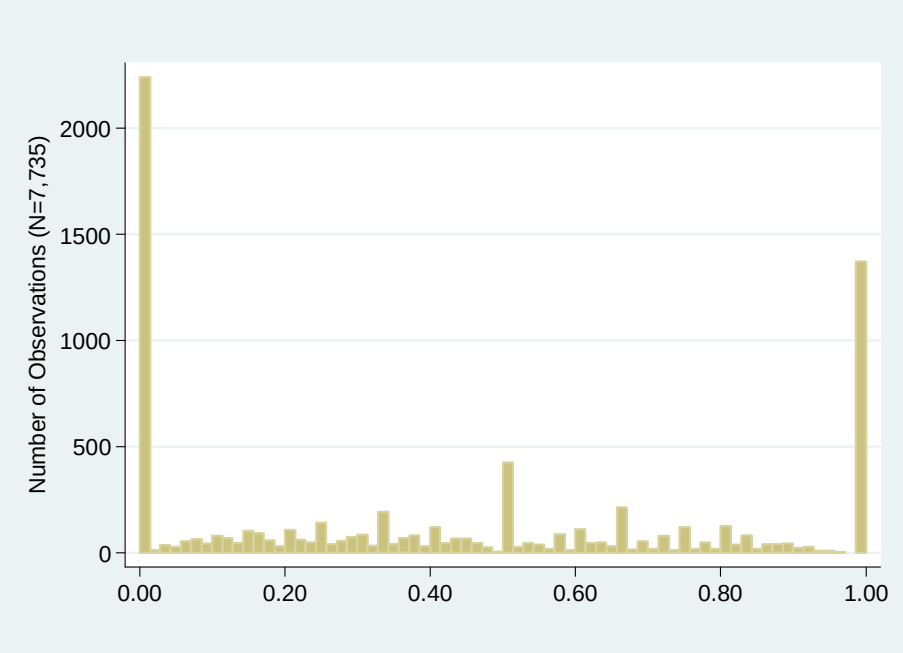


Figure 3. Proportion of clinical trials, by measures of novelty.

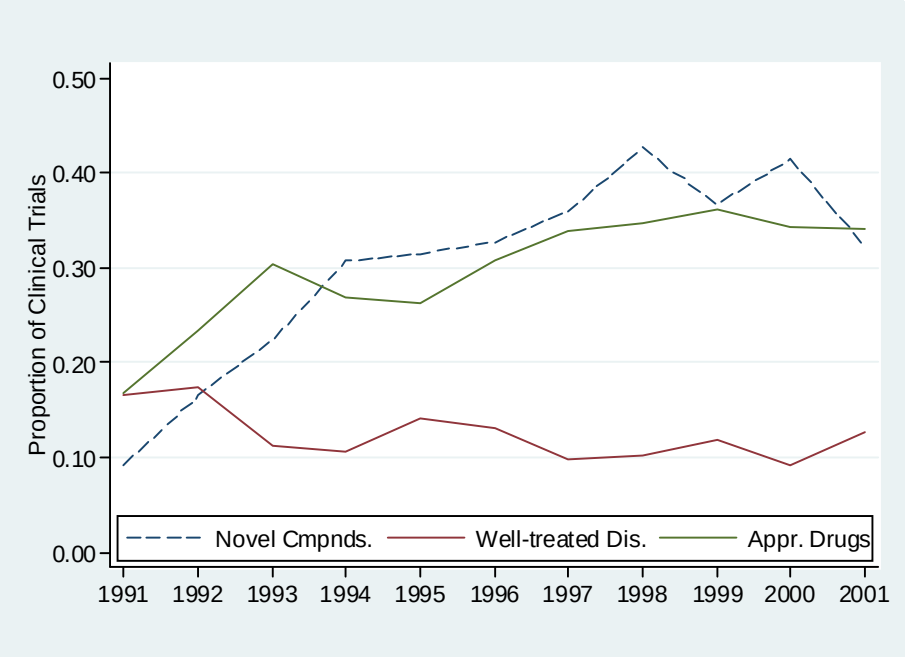


Figure 4A. Cumulative number of academic clinical sites, 1991-1999, by county

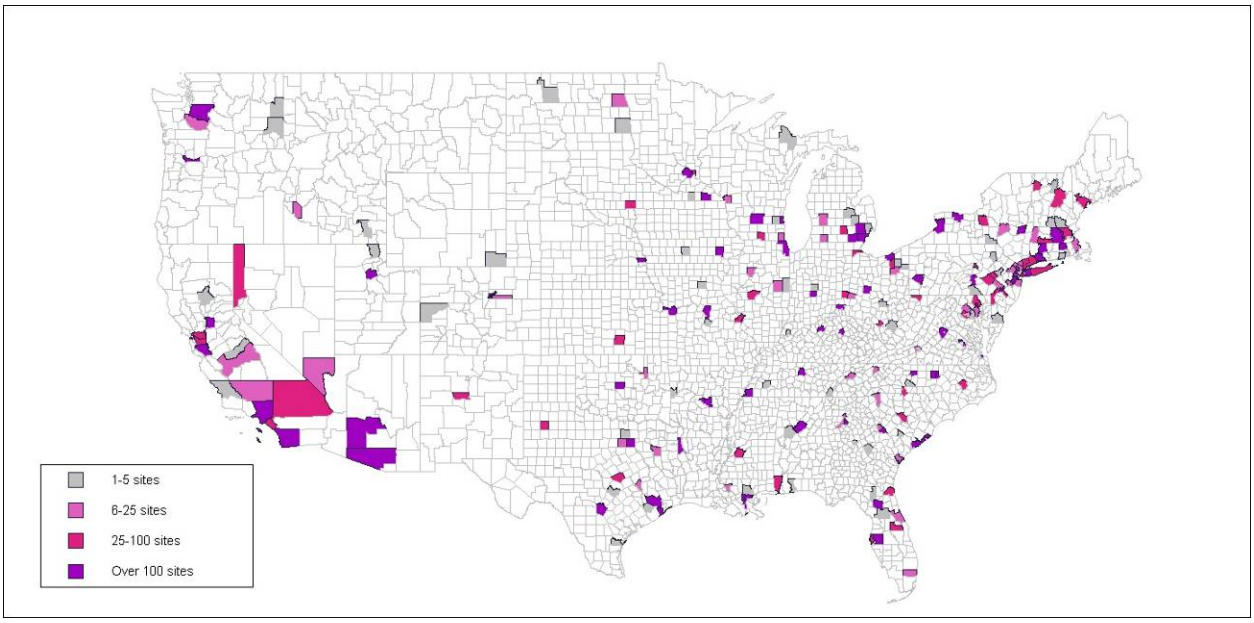


Figure 4B. Cumulative number of for-profit clinical sites, 1991-1999, by county.

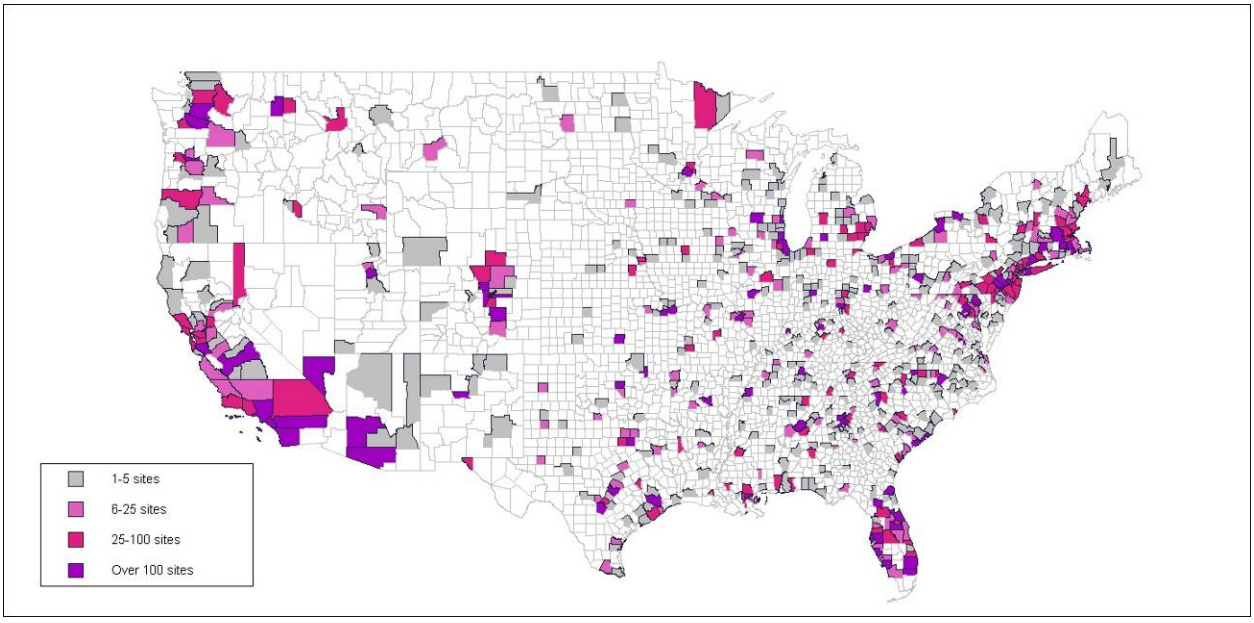


Figure 5. Distribution of mean annual number of clinical trial contracts by county.

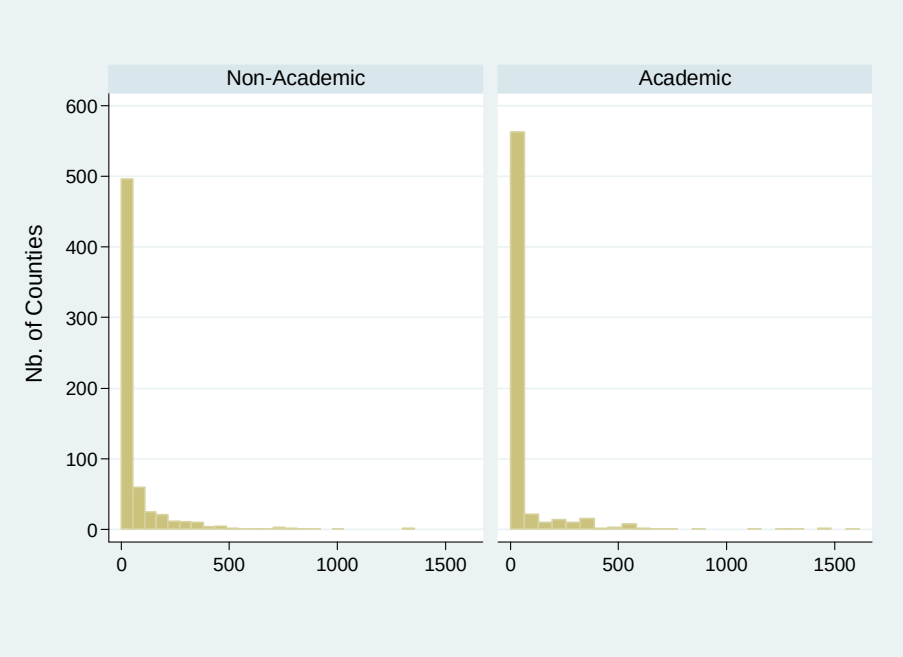


Figure 6. Annual county-level growth in HMO enrollment.

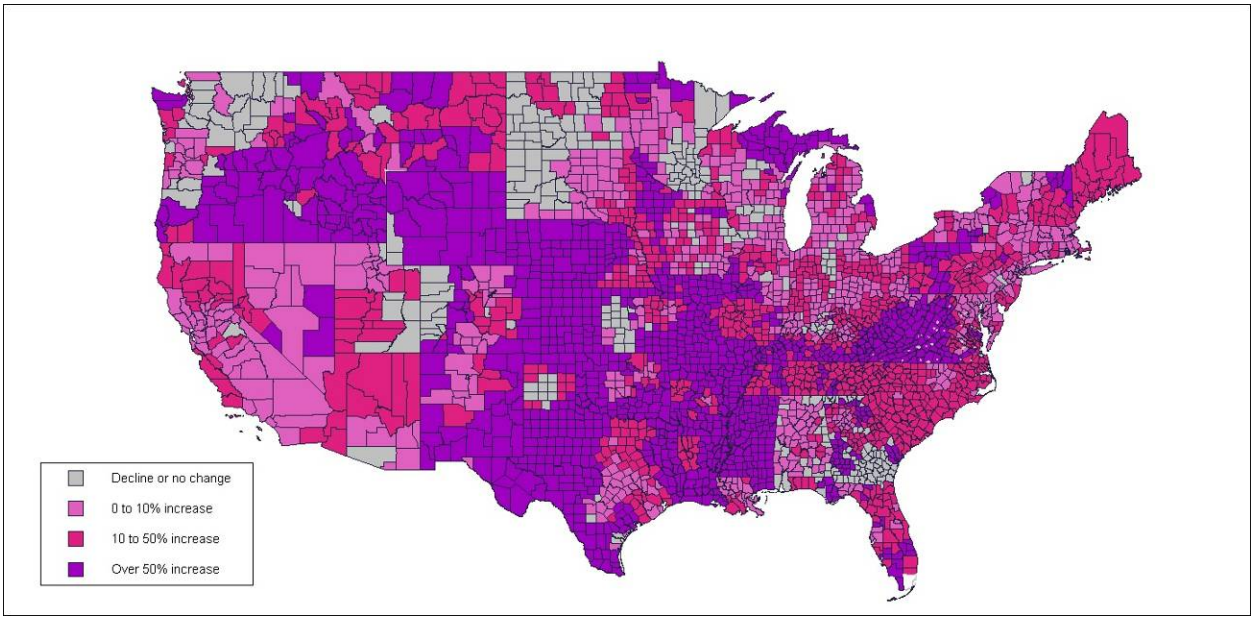


Figure 7. Clinical research reimbursements incorporate rents.

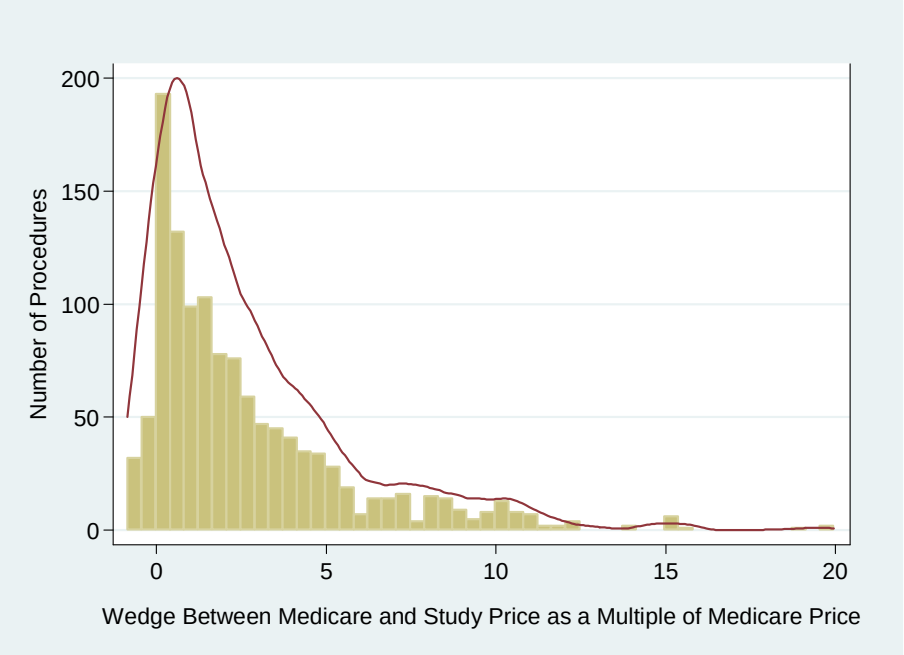
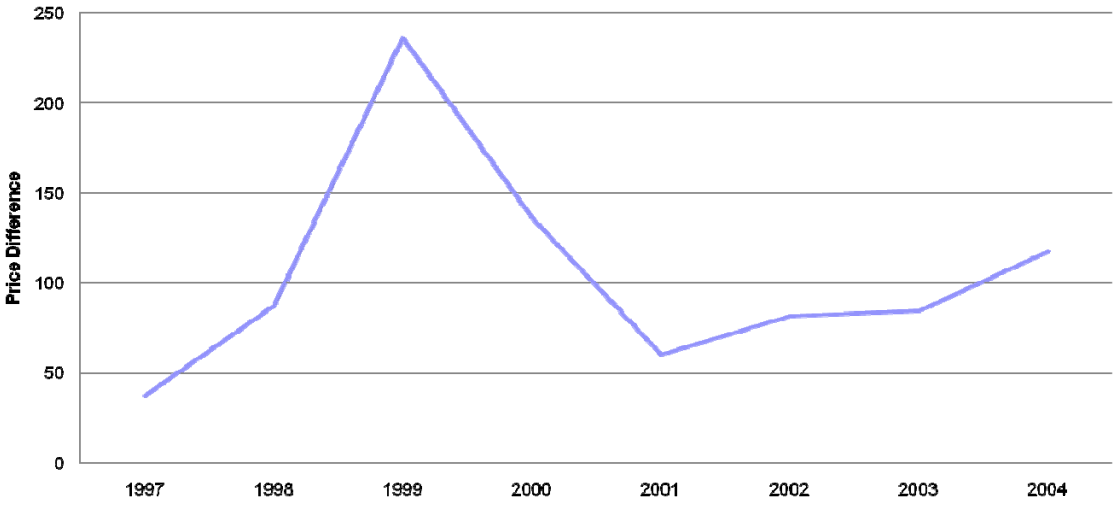


Figure 8. Medicare/clinical research price wedge.



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 η_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 η_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 β. The efficient two-step weight matrix W_N is given by

$$W_N(\widehat{\beta_1}) = \frac{1}{N}\sum_{i=1}^{N} g_i(\widehat{\beta}_1)g_i(\widehat{\beta}_1)^{'} \tag{II.4}$$

where

$$g_i = Z_i\left(\frac{y_i - exp(X_i^{'}\widehat{\beta}_1)}{exp(X_i^{'}\widehat{\beta}_1)}\right) \tag{II.5}$$

and $\widehat{\beta_1}$ 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

$$y_{it} = exp(X_{it}^{'}\beta + \eta_i) + \varepsilon_{it} = \mu_{it}\nu_i + \varepsilon_{it} \tag{II.6}$$

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

$$E[y_{it}|\nu_i, X_{it}] = E\left[y_{it}|\nu_i, X_{i1}, \ldots, X_{iT}\right]. \tag{II.7}$$

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 η_i. However, the Poisson maximum likelihood estimator for β 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 β 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

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

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):

$$\frac{1}{N}\sum_{i=1}^{N}\sum_{t=1}^{T} Z_{it}\left(y_{it}-\mu_{it}\frac{\overline{y}_i}{\overline{\mu}_i}\right). \tag{II.9}$$

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 that 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

	(1)	(2)	(3)	(4)
	Cross-Section	Cross-Section	Cross-Section	Within
ln(population)	4.077**	5.322**	5.015**	12.063*
	[0.947]	[1.001]	[1.008]	[5.001]
ln(avg. income)	1.125*	1.856**	1.971**	-1.872*
	[0.509]	[0.542]	[0.543]	[0.921]
ln(pop. over 65)	-1.376**	-1.201**	-1.125**	-5.733**
	[0.287]	[0.284]	[0.285]	[2.132]
ln(pop. under 15)	-0.809	-1.025	-0.765	-7.374**
	[0.739]	[0.731]	[0.733]	[2.658]
ln(pop. non-white)	-0.111	-0.121	-0.123	-2.474†
	[0.105]	[0.103]	[0.103]	[1.428]
ln(#MDs, office-based)	-0.382	-0.032	0.007	1.342
	[0.264]	[0.251]	[0.245]	[0.911]
ln(#MDs, hosp/research)	0.034	-0.024	-0.035	-0.096
	[0.066]	[0.066]	[0.065]	[0.149]
ln(area in sq mi)	-0.318**	-0.253*	-0.254*	
	[0.110]	[0.109]	[0.109]	
ln(#small firms)		-1.548**	-1.381**	1.208
		[0.381]	[0.379]	[1.693]
Regulated State			1.821**	1.540**
			[0.267]	[0.250]
Regulated State × ln(#Small Firms)			-0.229**	-0.193**
			[0.031]	[0.028]
Constant	-24.292**	-35.058**	-37.737**	25.356
	[5.548]	[6.366]	[6.435]	[25.880]
R^2	0.675	0.679	0.688	0.326
Chi^2 test: Law Vars = 0			29.385**	25.535**

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.

	(1)	(2)
	AMCs	For Profit
ln(#HMO enrollees)	0.089	-0.006
	[0.107]	[0.114]
ln(population)	-3.998**	-0.639
	[0.590]	[0.717]
ln(avg. income)	-0.469**	0.625**
	[0.177]	[0.178]
ln(pop. over 65)	0.913**	-0.195
	[0.147]	[0.202]
ln(pop. under 15)	2.301**	0.847*
	[0.355]	[0.426]
ln(pop. non-white)	-0.150*	-0.183**
	[0.061]	[0.050]
ln(#MDs, office-based)	0.007	0.561**
	[0.199]	[0.174]
ln(#MDs, hosp/research)	1.448**	0.186**
	[0.054]	[0.044]
ln(#small firms)	0.667**	0.513*
	[0.192]	[0.211]
ln(area in sq mi)	0.006	0.133**
	[0.028]	[0.040]
No of Observations	3,996	3,996
No of HSA/modified HSAs	444	444
Test of overidentifying restrictions, df=2	9.883**	0.343

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