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 preferred locus of industry-sponsored clinical trial activity. Instead, clinical trials have increasingly been conducted in private practices and for-profit, dedicated study sites. On the demand side, the greater availability of non-academic investigators enabled pharmaceutical firms to better match physicians' skills with specific projects. On the supply side, the growth of managed care health insurance has contributed to a rise in the number of physicians working in the for-profit clinical trials industry. Using a unique panel dataset based on information about 97,225 clinical trial contracts granted between 1991 and 2003, we first show that the proportion of academic investigators in a clinical trial correlates with project characteristics that plausibly proxy for the importance of knowledge-production activities. Second, we show that high managed care enrollment in a county is associated with more for-profit clinical research activity in that county, but not with academic clinical research in that same county. The result is strengthened when we instrument managed care enrollment with the passage of state-level "small group" insurance mandates.

Keywords: managed care, clinical trials, drug development.

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1 Introduction

Health policy researchers have long understood that particular 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, by highlighting how managed care health insurance has contributed to the rise of the "for-profit" clinical trial industry.

In order to gain regulatory approval for market introduction, the Food and Drug Administration (FDA) requires 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 provided by the results of randomized controlled trials (RCTs). In contrast to early-stage drug discovery research, 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. Over the past 15 years, however, academic organizations have gradually ceased to be the preferred locus of industry-sponsored drug development activities. Instead, clinical trials have been taking place in independent hospitals, private practices and for-profit, dedicated clinical research sites. During the 1990s, the proportion of academic clinical sites decreased steadily from 70% of U.S. sites in 1991 to 35% in 2001. What has caused this dramatic change in the organization of clinical development?

In a first step, we argue that 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 respond to this variation by fine-tuning the mix of academic and non-academic investigators to achieve an appropriate 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 relative importance of knowledge-production activities, relative to data-production activities.

In a second step, we study determinants of the supply of academic and for-profit clinical investigators by exploiting variation in research activity across geographic areas. The core of our argument is as follows. The gradual rise in managed care health insurance plans has eroded the personal income of physicians. Physicians, in response, have sought alternative sources of compensation, turning to clinical trials because reimbursements associated with treating "experimental patients" are higher than with those of managed care providers. However, this substitution incentive is muted in academia, since medical school faculty are typically not full residual claimants on the additional revenues corresponding to clinical trial contracts. Therefore, our hypothesis is that market penetration of managed care plans has been an important factor driving the shift in the relative supply of clinical investigators towards the non-academic sector.

In order to test this argument, we make use of a unique dataset of 97,225 clinical trial contracts granted between 1991 and 2003, which was supplied to us by Fast Track Systems, Inc. We first aggregate the data up to the clinical trial level and 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 (among others). Second, we aggregate the data up to the county-year level of analysis, and show that high managed care enrollment is associated with higher levels of non-academic clinical research activity in a county, but not with more academic clinical research in the same county. Because unobserved factors (such as variation in physician skills or in the competitiveness of the health care market) might lead managed care insurance companies and clinical investigators to cluster in similar geographic areas, these estimates suffer from endogeneity bias. As a result, we also present GMM estimates which rely on a plausibly exogenous source of variation in managed care enrollment: that induced by the passage of state-level "small group" insurance mandates throughout the 1990s. These estimates strengthen both the magnitudes and statistical significance of our core result.

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 develops the argument regarding plausible mechanisms linking managed care and clinical research activity. Section 4 describes the data, modeling approach, and identification strategy. Section 5 presents the main econometric results, while Section 6 offers some concluding remarks.

2 The rise of for-profit clinical research

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 file Investigational New Drug applications (INDs) with the FDA, granting them the authorization to begin testing in human trials for the compound's efficacy in treating a particular ailment, known as an "indication." 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), underscoring the risk inherent in the development process (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 product safety and efficacy, as gathered from the 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

[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).

drug approved for the treatment of morning sickness was 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 amendments. This Act of Congress required that new drugs be proven safe as well as effective to receive regulatory approval and established a legal framework for the subsequent acceptance of randomized controlled trials (RCTs) as the "gold standard" of evidence in clinical research. In addition to this substantive change, the agency 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 amendments 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).

Whether these formal rules arose from a compelling technical rationale or from the agency's desire to signal legitimacy to important constituents, their adoption into regulatory practice transformed the conduct of large scale clinical trials into a substantial organizational challenge. Since successful study completion requires a high degree of centralized planning, standardization, and coordination, pharmaceutical companies have invested substantially in the development of project management capabilities by assembling an in-house labor force capable of carrying out multi-center clinical studies.[2] Indeed, the large share of expenditures incurred outside the boundaries of pharmaceutical firms is a defining characteristic of clinical development.

Clinical trials are conducted by clinical investigators, which are physicians physically located at different research sites. Trials 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 circumstances idiosyncratic to a particular research site or physician. Long before formal testing requirements became enshrined into law, phar-

[2]In 1997, it was estimated that these tasks mobilized the effort of nearly 30% of overall industry personnel (PhRMA, 1999).

maceutical companies contracted out experimental human studies to clinicians. Pioneering examples of such collaborations include that of the Eli Lilly corporation and the University of Toronto for the development of insulin in the 1920s, and that of Merck with University of Pennsylvania researchers in the 1930s for the development of the anesthetic Vinethene (Swann, 1987). The phenomenon of using academic researchers reflected 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).

Today, clinical investigators operate out of a variety of different research sites: 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) and supported by analysis of the data used in this paper. 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.

2.1 Demand-side Considerations

The academic and non-academic sectors differ in the relative emphasis put on knowledge production (as opposed to data production) by clinical investigators. In addition to conducting industry-supported clinical trials, academic investigators also carry out "basic" clinical investigations, which are rewarded by publications, NIH grants, academic prestige, and promotion. In contrast, at commercial sites, investigators' allocation of effort is not lured away from data production by competing incentives. This diversity provides pharmaceutical firms with the opportunity to match carefully the composition of the investigator team with the types of problems most likely to arise during the clinical study. For example, when the

study examines a particular 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 there has been an industry-wide shift towards less knowledge-intensive clinical projects, then this shift could account for part of the observed change. Although a number of reports have emphasized the increasing prevalence of "me-too" drugs in corporate R&D strategies (NIHCM, 2002), the change in the investigator mix has been so drastic that demand-side explanations beg the question of why such matching of clinical investigators with project characteristics was not occurring earlier.

2.2 Supply-side Considerations

If one views RCTs as an innovation that any doctor is "at risk" of adopting at any particular point of time, then academics are akin to the "early adopters" and non-academics akin to the "late adopters" described by Rogers (1983) and other scholars of the diffusion of innovations. Certainly, the stock of potential investigators has increased over time as the medical school curriculum came to increasingly 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 10-year long effort to codify what had heretofore been informal agency practice. Culminating in the 1987 "IND/NDA rewrite," the new regulations added 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 exogenously lowered the costs of adoption for non-academic physicians, enabling them to

incorporate clinical research into their 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 constrained until the late 1980s. The cumulative effect of new cohorts of physicians familiar with RCTs, combined with the organizational template provided by the IND/NDA Rewrite relaxed this constraint and allowed pharmaceutical firms to better match investigators with projects. This explanation, while supported by anecdotal evidence, does not lend itself to empirical testing since it involves changes affecting the whole industry.

We focus instead on a different supply-side explanation, one that highlights the importance of a change affecting the provision of health care services: the rise of managed care health insurance. In the next section, we argue that, in recent decades, managed care has created downward pressures on physicians' personal incomes, and that these physicians are likely to try to meet income goals by substituting clinical trial patients for their former managed care 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 acceptance in the U.S. healthcare environment during the 1980s and 1990s.[3] 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. Its distinguishing features are usually some combination of the following: (1) selective contracting, whereby payers negotiate prices (often unilaterally) and selectively contract with local healthcare providers; (2) monetary and non-monetary incentives that steer enrollees towards the selected providers; (3) utilization reviews and controls that restrict the autonomy of 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

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

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. The growth of managed care gave physicians 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), and 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 now, 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. Evidence regarding the ability of managed care to alter the practice of medicine, however, has been more limited. Baker (1997; 1999), for example, has argued 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 or fee-for-service (FFS) patient population. First, managed care's presence in a geographic area creates a more competitive environment overall for the market prices charged for medical procedures. Second, managed care reduces the incentive (and available revenue) for a physician to invest in higher-cost technologies, which affects the technology's availability and therefore the likelihood that the physician will utilize it with his or her FFS patients. Finally, managed care spreads conservative behaviors and practice patterns such that a 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. Baker's argument is further supported in research conducted by Glied and Zivin (2002), who show that 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 credible source of exogenous variation to identify the effect of managed care penetration. This is essential for distinguishing causality from correlation, since managed care organizations are more likely to target areas in which medical expenditures (of which physician income is an important component) are already high or expected to increase. The lack of a consistent effect on physician income could also reflect demand inducement on the part of physicians among their non-capitated patients, whereby the quantity of services provided increases in response to a decrease in fees. 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 reducing expenditures through fee reductions (Gruber, Kim, and Mayzlin, 1999; Gruber and Owings, 1996; Leape, 1989; Yip, 1998).[4]

Collectively, 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 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 fee cut. 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 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, typically fee-for-service patients. But their work seems equally applicable to the case where the payers of interest are both private: managed care insurers and pharmaceutical firms who pay for services provided to patients enrolled in the clinical trials they sponsor. This substitution is plausible because

[4]Some policymakers have begun to incorporate 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, 1999).

clinical trials are a significant source of revenues, for which reimbursement levels remain similar to those of fee-for-service indemnity plans. 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).

What remains to be explained, however, is why the substitution patterns should differ across the academic and non-academic sectors. The main distinction between academic investigators and their colleagues operating 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 ban such financial incentives altogether 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, although such funds provide a valued source of financial support that supplements basic research.

Further, academic incentives have become ever more skewed against the performing of clinical trials by academic investigators. First, fellow academics sometimes view investigators with ties to industry as being "tainted," which has become increasingly true in light of recent scandals involving human subjects protection (Baird, Downie, and Thompson, 2002; Stelfox, Chua, O'Rourke, and Detsky, 1998). Second, whereas basic research makes unique demands on the creative and scientific potential of the investigator, clinical trials involve a substantial relinquishing of intellectual autonomy since the investigator must adhere to an agreed-upon plan of research designed by others. As a result, this activity does not produce rewards commensurate with those brought by other academic activities, such as publications and NIH grants, let alone intellectual satisfaction. This discussion suggests that more clinical trial activity will take place in high managed care penetration areas, but that this effect should be especially pronounced for non-academic clinical trial grants. If the pool of studies is fixed, one could even see managed care decreasing academic clinical research activity while increasing the number of non-academic grants. This should be true to the extent that

competition favors the type of firms who face higher-powered incentives at the margin: the non-academic, for-profit testing centers.

4 Data and Methodological Considerations

This section begins with a detailed description of the various data sources used in the paper, and is followed by a discussion of our econometric approach, including issues created by endogenous variables in count panel data models.

4.1 Data Sources, Sample Construction, and Descriptive Statistics

The core data source is a dataset of clinical investigator contracts made available by Fast Track Systems, Inc. Since the late 1980s, Fast Track has collected detailed information on clinical research from pharmaceutical companies. 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 represents 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. For purposes of the present study, each site was coded for its identity. 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 sites; all other sites (save for veterans hospitals unaffiliated with

[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 correspond to 82% of the aggregate amount reported by the Top 45 heaviest spenders.

medical schools and a few non-profit hospitals) were coded as non-academic, and 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 county level. This procedure yielded two distinct samples that we discuss in turn. **Project-level sample.** In addition to our dependent variable (the proportion of academic sites in a clinical trial), the data includes 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 reliably ascertain the academic status of clinical sites only for U.S.-based 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 reflected trials that were likely to be incomplete, yielding a final data set with 7,735 unique clinical trials. Descriptive statistics for this sample are displayed on Table 1A. As can be seen in Figure 1, 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 $]0;1[$. Modeling the determinants of a fractional outcome poses a number of econometric challenges that we discuss below.

County-level sample. Gross revenue and number of contracts for each clinical site was aggregated at the county-year level to create a panel data set of academic and non-academic clinical research dollars and contracts.

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.[6] 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 note 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.[7]

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. Number of physicians by county, in private practice or in academia, stem from the Area Resource File. Average income by county originates from the Bureau of Economic Analysis at the U.S. Department of Commerce.

Finally, data to support our instrumental variable strategy (explained below) stem from two sources: the size distribution of firms, collected from the census bureau's annual County Business Patterns file, and 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 Kosali 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,

[6]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 small number of changes in county borders between 1991 and 1999; market share and population information was generally allocated to 1991 geographic boundaries

[7]Because the HMO data ends in 1999, the clinical trial level information stems from a more restricted set of 61,352 investigator contracts signed between 1991 and 1999 (vs. 2003 as an end-date in the project-level sample).

2005; Hing and Jensen, 1999; Simon, 2005).[8] A similar table of state laws is listed on the web site of the Blue Cross and Blue Shield Association (BCBSA).

We display a graph of the county distribution of Average HMO penetration over the period 1991-1999 in Figure 2. This distribution is skewed, consistent with the fact that managed care activity tends to be clustered geographically. Figure 3 displays the evolution of the average county-level HMO penetration between 1991 and 1999, along with similar trends for the 10th and 90th percentile of this variable. Clearly, the 1990s saw a diffusion of managed care insurance — a key requirement for our study, which focuses both on cross-sectional and longitudinal patterns.

We turn our attention to the dependent variables in Figures 4 through 7. Figures 4 and 5 document a fact that motivates this paper: While the number of contracts for research conducted at academic sites has remained mostly stable throughout the 1990s, the number of contracts at non-academic sites has increased markedly. This pattern is also present, albeit less pronounced, when examining inflation-adjusted expenditures instead of the number of contracts. Figures 6 (resp. 7) display the county-level distribution of the number of contracts (resp. expenditures) between 1991 and 2001, broken down by affiliation status. In this analysis, as in the multivariate results below, we exclude any county in which there is no clinical tria l activity during the whole period. The distribution for both these variables is more skewed for academic sites, because the number of counties in which a teaching hospital or a medical school is present is of course a relatively small subset of the counties in which clinical research is conducted.

Descriptive statistics for the variables in the county-level sample are displayed in Table 1B.

4.2 Econometric Considerations

Project-level sample. To ascertain whether pharmaceutical firms' reliance on academic investigators is influenced by the importance of knowledge-production activities, relative to

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

data-production activities, we model the determinants of the fraction of academic investigators in a clinical trial, $\%AMC$, using the fractional logit estimator of 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.

County-level sample. We first examine the determinants of HMO enrollment across and within counties. To do so we regress the log of the number of HMO enrollees on county 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 in a county, or the amount of clinical research expenditures in a county) makes the use of traditional least squares regression techniques problematic. The distribution of these variables exhibit a large mass point at 0 (see Figures 5 and 6). 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 county 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.[9]

Endogeneity of HMO Enrollment. Of course, the structure of the health insurance industry and entry into the clinical research industry could be jointly determined. Both

[9]In fact the PQML estimator can be used for any non-negative dependent variables, whether integer or continuous (see Santos-Silva and Tenreyro, 2006).

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.

Past researchers have long been aware of this problem, but their efforts 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.[10]

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 —

[10]There is another drawback to the use of the size distribution of firms as instrumental variables: While it is indeed associated with HMO penetration in the cross-sectional dimension, it is a relatively stable characteristic of geographic areas, and hence not highly correlated with changes in HMO market share. This drawback precludes their use in within-county specifications.

i.e., employees of small firms — is less predictable, so small employers tend to be forced 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 effect of the legal environment influence the market for clinical research only through its effect on HMO enrollment. This maintained assumption forms the basis of our identification strategy.

We construct 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 county. 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). Admittedly, these legislative events would probably not be suitable for a study of the effect of HMO penetration on physician incomes or health care quality. However, the possibility that these laws — which focus entirely on the structure of the insurance industry — are endogenous to the market structure of the clinical trials industry appears remote. The content of the laws and the construction of the instruments are explained in more detail in Appendix I.

Skewed outcomes and IV estimation. Following the notation of Windmeijer (2005), we choose to write our basic model:

$$y_i = exp(X_i^{'}\beta) = \mu_i\nu_i = exp(X_i^{'}\beta + \eta_i)$$

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

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

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 (1) is no longer consistent. If there are instruments Z available then

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

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

$$Q_N(\beta) = \left(\frac{1}{N}\sum_{i=1}^{N} g_i\right)^{'} W_N^{-1}\left(\frac{1}{N}\sum_{i=1}^{N} g_i\right)$$

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

$$W_N(\widehat{\beta}_1) = \frac{1}{N}\sum_{i=1}^{N} g_i(\widehat{\beta}_1)g_i(\widehat{\beta}_1)^{'}$$

where

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

and $\widehat{\beta}_1$ an initial consistent estimator. The GMM estimates presented below use the moment conditions in (2), where the instrument vector Z contains exogenous county and state characteristics (population, average income, etc.) and the two excluded instruments mentioned above. A similar approach can be applied to within-county models, in the spirit of the fixed effect Poisson model of Hausman, Hall, and Griliches (1984). The derivation of the appropriate moment conditions is detailed in Appendix II.

5 Results

5.1 The demand-side: Matching investigators with projects

We begin by presenting the results of our analysis of the project-level sample. Of course, the credibility of this exercise hinges on our ability to distinguish empirically between knowledge-intensive and data-intensive projects. Fortunately, the dataset contains a rich set of characteristics that can plausibly proxy for the relative importance of knowledge-intensive activities. We begin by measuring the inovativeness of the project in three distinct ways. *FDA Approved* indicates whether the drug was approved for use at the beginning of the clinical trial. 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. In this 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.

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 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.

[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 icd9 codes and associated drugs provided by Frank Lichtenberg.

Results from these analyses can be found in Table 2. 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 inovativeness. The three measures of inovativeness 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 (Cockburn et al., 2000). Model (5) alleviates this concern by adding to the specification a full set of firm fixed effects. The results are qualitatively similar, although the measure of inovativeness based on FDA approval loses statistical significance in this more demanding specification.

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.

5.2 The supply-side: The effect of managed care and changing physicians' incentives

We begin by reporting results from a first-stage analysis of the determinants of HMO enrollment between and within counties in Table 3. 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 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 (Buchmueller and Liu, 2005). 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. This assumption seems reasonable in light of the fact that these laws were enacted because of concerns regarding the *downstream* pricing and delivery of health care services, and not because of concerns regarding *upstream* health care R&D.

Table 4 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. Columns (1) and (2) show that HMO enrollment is more strongly correlated with non-academic clinical research than with academic clinical research. At the mean of the data, increasing HMO enrollment from the 50^{th} to the 75^{th} percentile (approximately from 22,500 enrollees to 80,000 enrollees) increases the predicted number of non-academic clinical trial contracts in the county from 2.18 to 2.66, a 22.16% increase. The comparable magnitude for academic sites is 7.36% and the corresponding estimate is statistically significant from 0 only at the 10% level.

As emphasized above, these pooled cross-sectional estimates cannot be given causal interpretations because HMO enrollment and clinical research activity might be jointly determined. To tackle this endogeneity problem, we estimate these same models using the generalized method of moments and the "small group" instruments in columns (3) and (4). Under the assumption that these two variables are legitimately excluded from our second stage, the resulting estimates should be consistent. In column (3), we see that purging the naïve Poisson estimates from endogeneity bias strengthens both the magnitude and the statistical significance of the effect of HMO enrollment on "for-profit" clinical trial activity. In contrast, column (4) shows that the effect on academic clinical research flips sign compared to column (4), and is no longer statistically significant at conventional levels. In both models, the results of the test of overidentifying restrictions imply that we cannot reject the joint null hypothesis that the excluded instruments are uncorrelated with the error term and correctly excluded from the estimated equation.

To summarize, it does not appear that the findings of columns (1) and (2) are merely artefact of endogenous locational choice by HMOs and physicians. On the contrary, the

evidence shows that managed care health insurance created incentives for physicians to substitute "experimental patients" for HMO patients, as reimbursements for the former are widely perceived as incorporating rents. 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.

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.

6 Conclusion

We study the mix of academic of non-academic investigators chosen by pharmaceutical firms to perform the clinical trials they sponsor, and show that this mix is sensitive to the relative importance of two activities that compete for investigators' attention: knowledge production and data production. Yet, the emergence of a "for-profit" clinical trials industry is a relatively recent phenomenon. Since matching physicians' skills with the correct projects was presumably as valuable in the past as it is today, to explain this trend we must identify the features of the institutional environment that have changed in the same period.

We regard the explanation that the project portfolios of pharmaceutical firms have shifted decisively towards so-called "me-too" projects as *a priori* implausible. It is true that success

with such projects is more sensitive to data-production effort than knowledge-production effort (which might favor the recruitment of non-academic investigators). But even if a shift occurred in this direction, its magnitude was modest and could not, by itself, have accounted for the drastic expansion of clinical research outside of academia.

We focus instead on a shift in the relative supply of academic and non-academic investigators over time, induced by the growth of managed care insurance plans. We show that within states, counties with high HMO enrollment also see more "for-profit" clinical research activity, but do not see more academic clinical research activity. Moreover, this relationship appears causal: our estimates are strengthened when instrumenting HMO enrollment with the passage of "small group" insurance mandates at the state level.

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).

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Figure 1: Proportion of Academic Investigators within a Clinical Trial

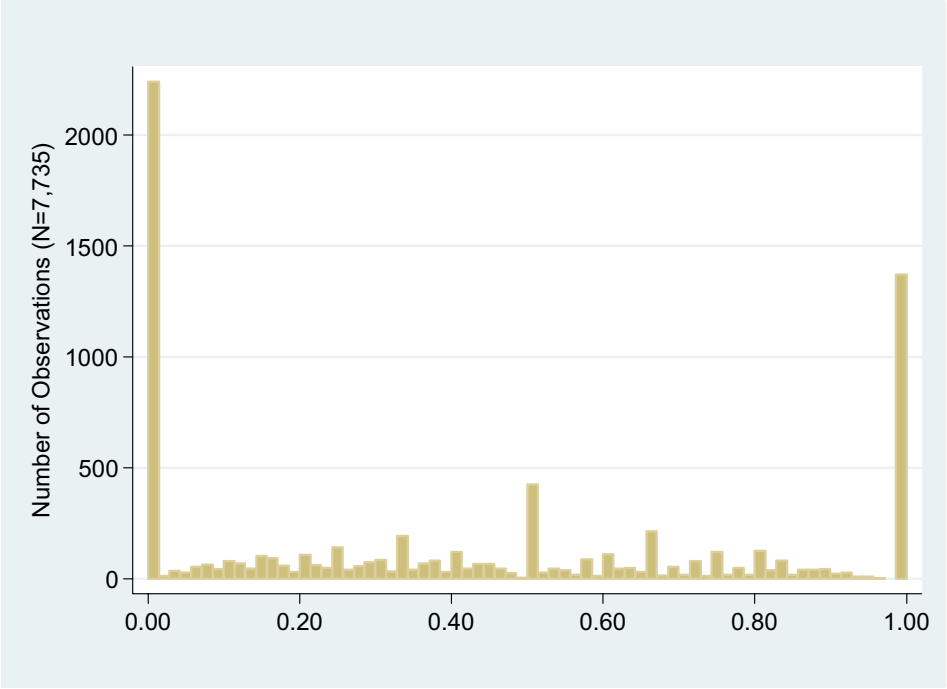

Figure 2: Distribution of County-level Mean HMO Penetration, 1991-1999.

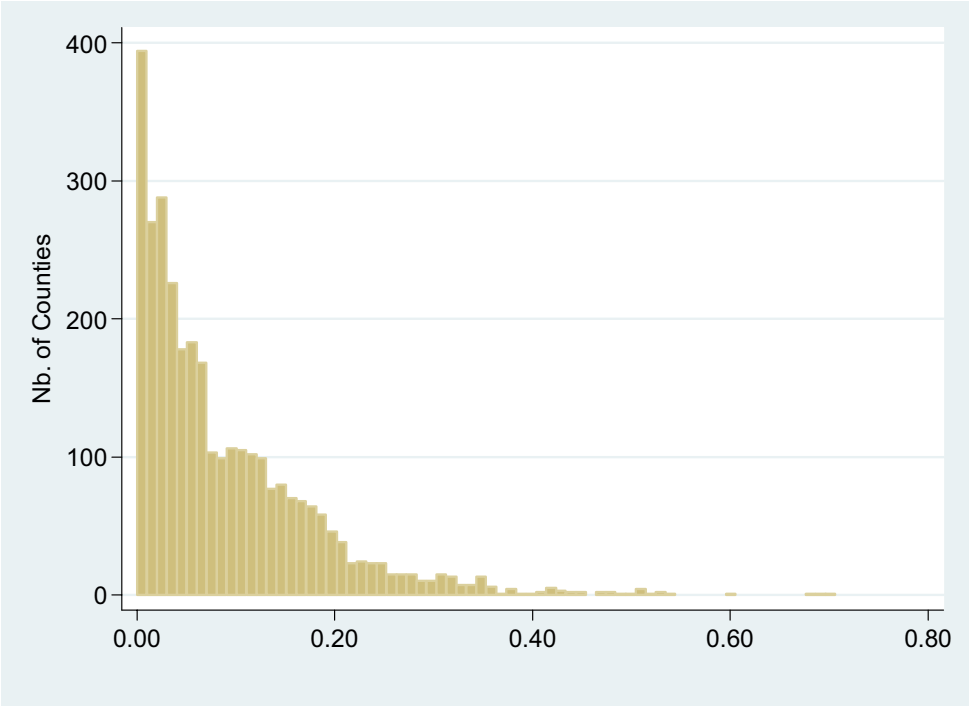

Figure 3: Trends in HMO Penetration, 1991-1999.

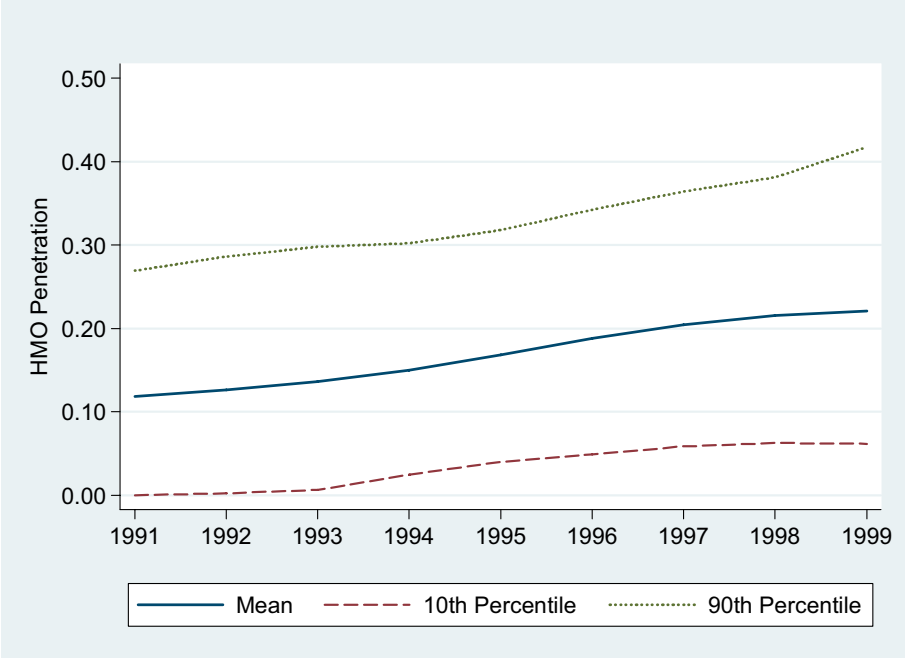

Figure 4: Clinical Trial Contracts by Academic Affiliation, 1991-2001

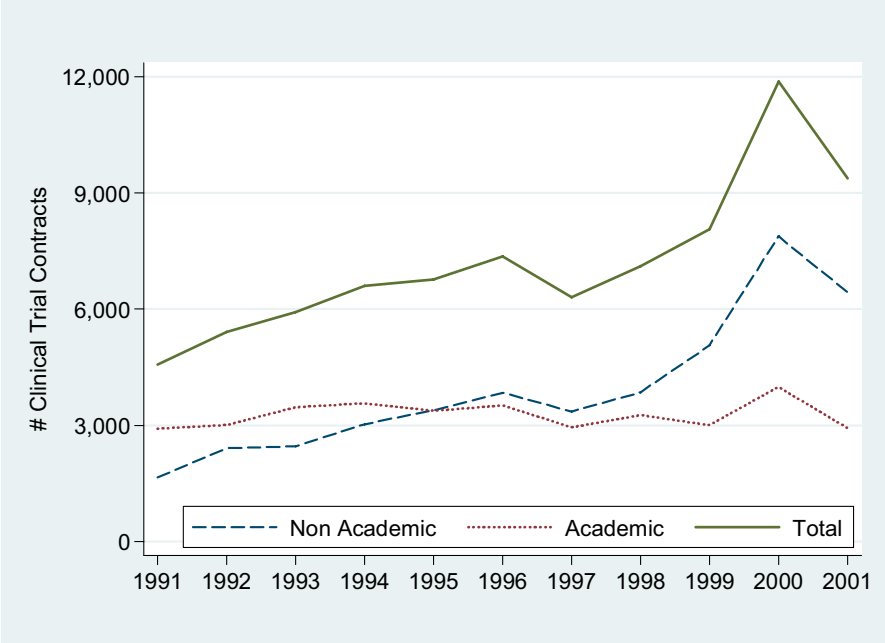

Figure 5: Clinical Trial Expenditures by Academic Affiliation, 1991-2001

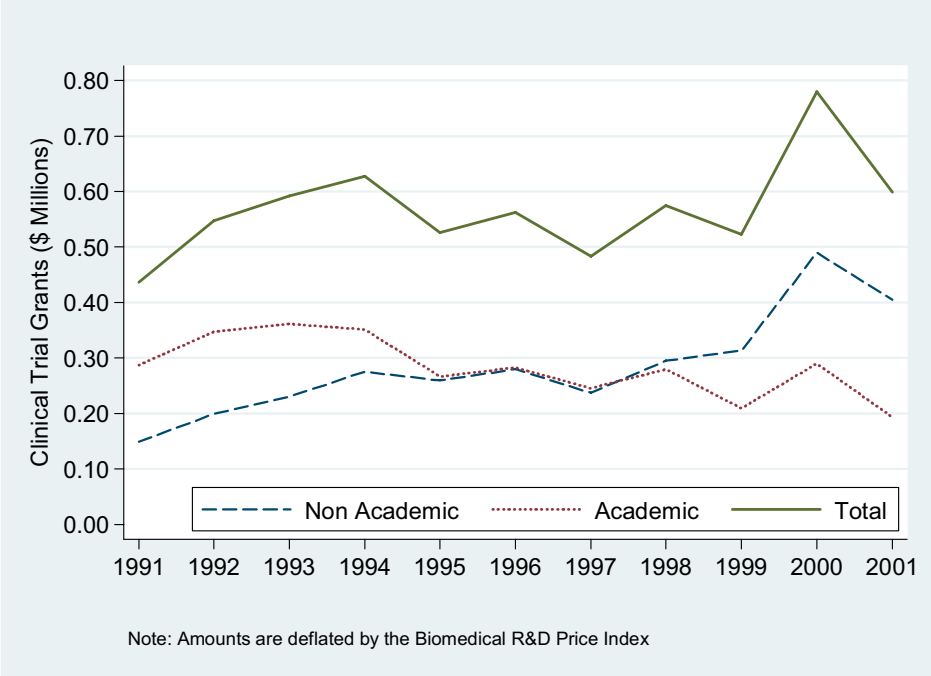

Figure 6: Distribution of Total Clinical Trial Contracts by County

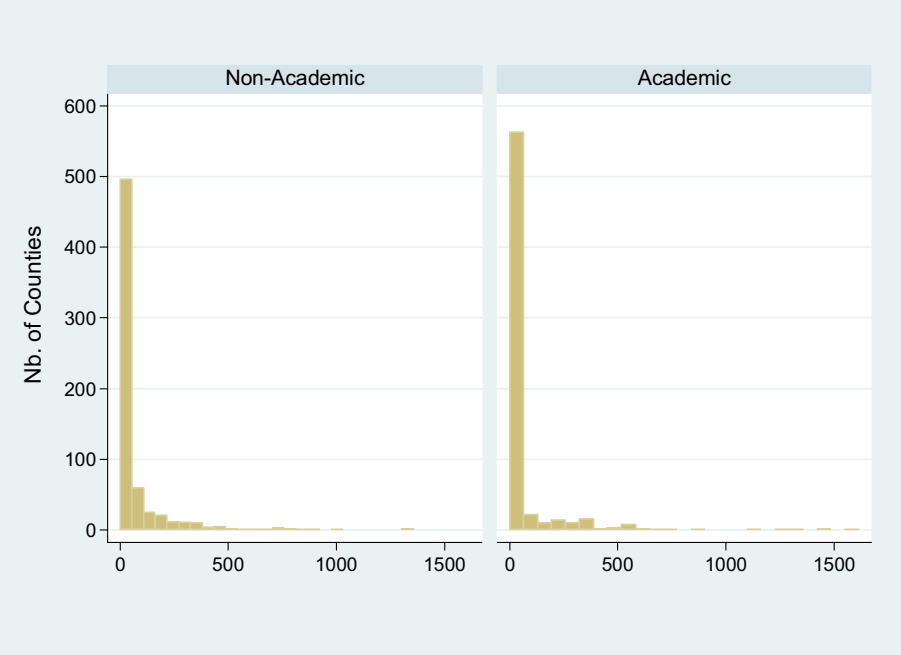

Figure 7: Distribution of Total Clinical Trial Expenditures by County

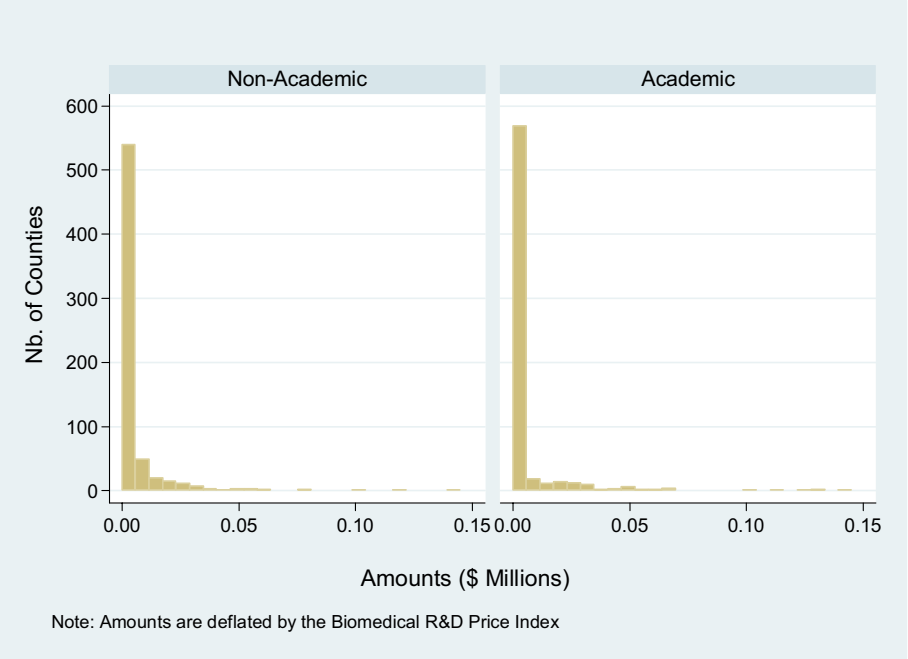

Table 1A: Descriptive Statistics, Project-level Sample

	Nb. Obs	Mean	Std. Dev	Min.	Max.
%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 I (Oncology)	7,735	0.041	0.197	0	1
Phase I (Other)	7,735	0.312	0.463	0	1
Phase II	7,735	0.220	0.415	0	1
Phase III	7,735	0.358	0.479	0	1
Phase IV	7,735	0.069	0.254	0	1
Nb. of Procedures	7,735	77.602	66.358	1	909
Outpatient	7,735	0.615	0.487	0	1
Trial Length (in weeks)	7,735	20.586	33.579	0.14	520

Table 1B: Descriptive Statistics, County-level Sample

	Mean	Std. Dev	Min.	Max.
Non-Academic Sites	5.765	13.216	0	149
Academic Sites	5.768	17.151	0	166
HMO Enrollees (×1,000)	82.818	232.223	0	5,595
Population (×1,000)	337.443	582.247	10	9,330
Average Income (×1,000)	23.067	6.148	10	80
Population over 65 (×1,000)	41.696	67.352	0	969
Population under 15 (×1,000)	72.715	131.513	2	2,157
Population Non-white (×1,000)	103.504	319.886	0	6,239
Nb. of MDs, Office-based	644.909	1,185.871	3	17,165
Nb. of MDs, Hosp. Research & Teaching	38.661	100.011	0	1,119
Nb. of Small Businesses	5,397.301	9,113.930	88	99,587
Small Group Mandates	1.024	0.906	0	2

N = 5,040 county-year observations (560 counties × 9 years).

Table 2: Determinants of %AMC (QML Fractional Logit Estimates)

	(1)	(2)	(3)	(4)	(5)
FDA approved	-0.138*			-0.152*	-0.089
	[0.068]			[0.067]	[0.064]
First-in-Class		0.334**		0.378**	0.259*
		[0.109]		[0.107]	[0.103]
Well-Treated Disease			-0.588**	-0.617**	-0.655**
			[0.089]	[0.089]	[0.084]
Phase I (Oncology)	1.082**	1.127**	1.155**	1.162**	1.230**
	[0.200]	[0.203]	[0.200]	[0.202]	[0.196]
Phase II	0.990**	1000**	1.043**	1.020**	0.952**
	[0.089]	[0.089]	[0.088]	[0.088]	[0.084]
Phase III	0.583**	0.571**	0.636**	0.636**	0.599**
	[0.091]	[0.092]	[0.091]	[0.091]	[0.086]
Phase IV	0.777**	0.717**	0.793**	0.857**	0.800**
	[0.122]	[0.123]	[0.122]	[0.121]	[0.118]
Ln(Nb. of Procedures)	0.014	0.021	0.028	0.024	0.032
	[0.030]	[0.030]	[0.029]	[0.029]	[0.029]
Outpatient	-0.343**	-0.342**	-0.291**	-0.288**	-0.282**
	[0.078]	[0.079]	[0.078]	[0.078]	[0.074]
Ln(Length of Protocol)	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 Quasilikelihood	-4129.86	-4125.01	-4111.02	-4098.14	-3963.91
Nb. of Observations	7,703	7,702	7,703	7,700	7,612

Dependent variable is the percentage of academic sites in a clinical trial. All models report heteroskedasticity-robust standard errors, clustered by chemical compound. All models contain fourteen therapeutic class effects (with oncology being the omitted class) and year effects. Models with first-in-class variable include dummy variable (not reported) for "rating unavailable" category. Omitted phase dummy is Phase I (Other).

† significant at the 10% level
* significant at the 5% level
** significant at the 1% level

Table 3: Determinants of HMO Enrollment (OLS Estimates)

	(1)	(2)	(3)	(4)
Ln(Nb. Small Firms)		-1.323*	-1.202*	0.362
		[0.275]	[0.278]	[0.923]
Regulated State			1.198*	1.251*
			[0.232]	[0.226]
Regul. State × Ln(Nb. Small Firms)			-0.147*	-0.153*
			[0.027]	[0.026]
Ln(County Population)	2.444*	3.760*	3.657*	5.379
	[0.742]	[0.804]	[0.809]	[3.436]
Ln(County Average Income)	1.340*	1.895*	1.952*	-0.777
	[0.385]	[0.375]	[0.380]	[1.035]
Ln(County Population, Over 65)	-0.812*	-0.775*	-0.771*	-2.267*
	[0.215]	[0.205]	[0.205]	[1.067]
Ln(County Population, Under 15)	0.176	-0.159	-0.048	-4.425†
	[0.579]	[0.576]	[0.581]	[2.328]
Ln(County Population, Non-white)	0.006	-0.022	-0.030	-1.316
	[0.094]	[0.091]	[0.092]	[1.322]
Ln(#MDs, Office-based)	-0.596*	-0.235	-0.223	1.179*
	[0.134]	[0.145]	[0.147]	[0.502]
Ln(#MDs, Hosp. Res. & Teaching)	0.114*	0.060	0.063	-0.102
	[0.057]	[0.056]	[0.056]	[0.151]
Constant	-23.976*	-32.740*	-34.339*	24.642
	[3.806]	[4.026]	[4.116]	[16.016]
County Fixed Effects	No	No	No	Yes
R^2	0.649	0.655	0.659	0.207
F-test: Law Vars. = 0			14.89**	19.04**

Regressions contain 5,040 county-year observations. Pooled cross-section models (columns 1, 2, and 3) contain year and state fixed effects. Within-county model (column 4) contains year fixed effects. Heteroskedasticity-robust standard errors are in brackets, clustered by county.

† significant at the 10% level
* significant at the 5% level
** significant at the 1% level

Table 4: HMO Enrollment and the "For-Profit" Clinical Trial Industry: Pooled County Cross-section Models.

Dependent variable is the number of clinical trial contracts in a county/year.

	(1)	(2)	(3)	(4)
	Poisson QML		GMM	
	Non-Academic	Academic	Non-Academic	Academic
Ln(#HMO Enrollees)	0.158*	0.056†	0.432**	-0.108
	[0.070]	[0.031]	[0.057]	[0.348]
Ln(County Population)	-1.145	-1.489	-2.660**	0.372
	[1.093]	[1.227]	[0.686]	[1.751]
Ln(County Average Income)	-0.554†	-1.403**	-0.145	-0.906
	[0.328]	[0.477]	[0.354]	[0.553]
Ln(County Population, Over 65)	0.154	0.298	1.109**	0.256
	[0.306]	[0.284]	[0.236]	[0.273]
Ln(County Population, Under 15)	0.452	0.201	0.509	-0.689
	[0.851]	[0.843]	[0.552]	[0.742]
Ln(County Population, Non-white)	-0.271*	0.212†	-0.409**	0.165
	[0.110]	[0.112]	[0.080]	[0.101]
Ln(#MDs, Office-based)	0.230	-0.509	0.122	0.287†
	[0.256]	[0.440]	[0.147]	[0.169]
Ln(#MDs, Hosp. Res. & Teaching)	0.259*	1.277**	0.355**	1.121**
	[0.118]	[0.135]	[0.049]	[0.073]
Ln(#Small Firms)	1.304**	1.027*	1.582**	-0.307
	[0.336]	[0.454]	[0.314]	[0.547]
Constant	1.917	15.58**	3.323	7.128
	[3.536]	[5.487]	[4.163]	[9.883]
Log Quasilikelihood	-16,080.20	-7,326.36		
Test of Overid. Restrictions			2.212	1.421
(df = 2)			p=[.33]	p=[.23]
Number of Observations	5,040	1,845	5,040	1,845

All models contain year and state effects; Heteroskedasticity-robust standard errors in brackets, clustered by county.

† significant at the 10% level
* significant at the 5% level
** significant at the 1% level

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 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:
Estimation of Within-County Models with Endogenous Regressors

Let y_{it} denote the skewed outcome to be expplained 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 modelled multiplicatively as

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

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

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

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 (2005: 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

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

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.1):

$$\frac{1}{N}\sum_{i=1}^{N}\sum_{t=1}^{T} Z_{it}\left(y_{it} - \mu_{it}\frac{\overline{y}_i}{\overline{\mu}_i}\right). \tag{II.2}$$

Table 5 presents estimates based on these moment conditions. We find no evidence of any influence of HMO enrollment on clinical research activity in the within-county dimension of the data. This is true whether we focus on the Poisson conditional quasi-maximum likelihood estimates [columns (1) and (2)], or whether we estimate these models using GMM [columns (3) and (4)). Similarly, we see no difference between the response of academic and non-academic investigators within county. Because we know [from Table 3, Model(4)] that our instruments are correlated with HMO enrollment within county, we can only surmise that there is not enough within-county variation in clinical research activity to identify effects such as those found in Table 4.

Table 5: HMO Enrollment and the "For-Profit" Clinical Trial Industry: Within-County Models.

Dependent variable is the number of clinical trial contracts in a county/year.

	(1)	(2)	(3)	(4)
	Poisson CQML		GMM	
	Non-Academic	Academic	Non-Academic	Academic
Ln(#HMO Enrollees)	0.014	0.010	0.065	0.048
	[0.035]	[0.012]	[0.073]	[0.031]
Ln(County Population)	-0.864	-1.681	-1.362**	-0.783**
	[2.357]	[1.128]	[0.382]	[0.176]
Ln(County Average Income)	-2.683**	-0.015	-3.084**	0.030
	[0.497]	[0.355]	[0.349]	[0.211]
Ln(County Population, Over 65)	0.276	0.391	1.400†	1.568**
	[0.587]	[0.439]	[0.734]	[0.322]
Ln(County Population, Under 15)	0.815	1.796**	-0.033	-0.772**
	[1.111]	[0.493]	[0.418]	[0.191]
Ln(County Population, Non-white)	0.278	-0.469	0.616†	0.010
	[0.687]	[0.502]	[0.372]	[0.200]
Ln(#MDs, Office-based)	0.571	0.557*	0.714**	0.263*
	[0.349]	[0.270]	[0.247]	[0.122]
Ln(#MDs, Hosp. Res. & Teaching)	-0.113	0.276**	-0.161*	-0.027
	[0.104]	[0.102]	[0.073]	[0.062]
Ln(#Small Firms)	-0.210	-0.641	-0.463	-0.910**
	[0.752]	[0.488]	[0.477]	[0.263]
Log Quasilikelihood	-7,223.61	-3,464.23		
Test of Overid. Restrictions			73.42	77.90
(df = 2)			p=[.71]	p=[.58]
Number of Observations	4,860	1,845	4,860	1,845

All models contain year effects. Heteroskedasticity-robust standard errors in brackets, clustered by county.

† significant at the 10% level
* significant at the 5% level
** significant at the 1% level