The Effect of Insurance on Disparities in Trial Enrollment*

Jennifer Kao
UCLA Anderson

Tamar Oostrom
The Ohio State University

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Abstract

We investigate the causes and consequences of demographic disparities within pharmaceutical innovation process. We focus on how insurance coverage policies affect elderly enrollment in clinical trials. Beginning in 2000, Medicare expanded coverage for the routine costs of enrolling in clinical trials. This policy change led to a shift in the rate and direction of clinical trial activity: there was a significant increase in the number of clinical trials targeting diseases common among the elderly population, relative to diseases common among the non-elderly. Our findings indicate that trial sponsors modified enrollment criteria to include more elderly participants, leading to increased participation. The effects of this shift appear to be large. After the Medicare policy, there is a disproportionate increase drug utilization among the elderly for diseases where there was an increase in their representation.

JEL Classifications: O31, O38, I14, I18
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1 Introduction

During research and development (R&D), firms must decide which user groups to engage with to develop, prototype, and test their products. While diverse representation may support the innovation of new products targeted at these groups and spur product adoption, recruiting diverse participants may require additional costs, more complicated logistics, and building trust with participants. This paper studies how financial frictions shape representation in R&D and how representation affects product adoption.

We focus on drug development, where firms enroll participants in clinical trials to generate information about a drug's safety and efficacy. Historically, elderly, women, and Black clinical trial participants were often underrepresented in diseases relative to disease burden. For example, elderly individuals make up nearly 63 percent of new cancer cases, but only comprise 25 percent of participants in cancer clinical trials (Hutchins et al., 1999). Financial barriers are frequently cited as a significant obstacle to enrollment in clinical trials, alongside other factors such as misconceptions about the benefits of clinical trials and the presence of coexisting medical conditions (Lara et al., 2001).

This paper investigates how expanding insurance coverage of clinical trials for elderly individuals affected innovation in elderly diseases, representation in clinical trials, and utilization of prescriptions by older individuals. In 2000, President Clinton passed an executive memorandum requiring Medicare to cover the routine patient costs associated with clinical trial participation (Charatan, 2000).[1] This policy was enacted in response to growing concerns that low clinical trial representation of participants aged over 65 may lead to delays in trial enrollment and ultimately higher costs of drug development. Prior to 2000, drug sponsors and Medicare patients had to pay for the routine patient costs of qualifying clinical trials. We use this variation to generate insights into the role of financial frictions in representation, relative to other key barriers such as trust (Alsan and Wanamaker, 2017), stereotypes (Hebert, 2019), and safety concerns Nadel (1992).

We leverage a difference-in-differences design, utilizing cross-disease variation in exposure to the Medicare policy, to examine the causal impact of the Medicare Memorandum of 2000 on drug development and adoption. In particular, we examine (1) the number of clinical trials targeting diseases common among the elderly, (2) the number of trials expanding their enrollment criteria to include the elderly and the number of elderly participants enrolled in these trials, and (3) the adoption rate of pharmaceuticals by elderly individuals for diseases common among the elderly. We assemble a new dataset of clinical trials spanning 1995 to 2010. We observe many characteristics of these clinical trials, including the trial start

[1] See the press release archived at https://clintonwhitehouse3.archives.gov/WH/New/html/20000607.html.

and end date, the diseases under investigation, the patient enrollment criteria used, and the number of elderly participants enrolled. Using data on drug utilization, we track how changes in clinical trials for specific diseases and drugs lead to alterations in the use of those drugs for those conditions.

Our findings suggest that the Medicare Memorandum of 2000 meaningfully shifted drug development. We find that diseases most affected by the memorandum experienced a 17 percent increase in the number of clinical trials, relative to diseases that were least affected. The increase in the number of clinical trial in elderly diseases occurs immediately after the memorandum, before Medicare Part D was introduced in January of 2006, or the law was signed in December of 2003. Our results are robust to both controlling for the passage of Part D and to excluding years after the passage of Part D.

We investigate whether this increase in elderly-focused innovation translated into changes in trial design and in elderly trial participation. We show that following the Medicare Memorandum of 2000, firms increased the number of clinical trials with patient enrollment criteria targeted towards the elderly among affected diseases by 27 percent. In contrast, the number of clinical trials with enrollment criteria that did not mention elderly participants remained constant. The expansion of enrollment criteria translated into an increase in the number of elderly trial participants. These results are economically significant: in 1999, the average number of elderly participants in a given trial targeting the elderly was 14. Sertkaya et al. (2016) estimate that average per-patient recruitment and retention costs per trial amount to $184,000, suggesting that the Medicare Memorandum of 2000 maybe save drug developers over $1.5 million for a single trial. This estimate is conservative as it does not take into account the increase in the number of clinical trials resulting from the Memorandum or the additional profits associated with accelerating the trial enrollment process faster.

The benefits of increased representation are most compelling if they shape patient outcomes. A recent literature has highlighted the role of representation in shaping product utilization. In related work, Aslan et al. (2022) provide survey results indicating that greater levels of black patient enrollment increases doctors' likelihood to prescribe drugs and affects black patients' views on the drugs' effectiveness. Consistent with these results, we find that following the memorandum, there was a disproportionate increase in drug utilization among elderly patients for elderly diseases, relative to both non-elderly diseases and non-elderly patients. This approach uses variation both across diseases in exposure to the memorandum and variation in the ages of individuals using these pharmaceuticals, adding another dimension of variation.

Our paper contributes to the literature on improving representation in research and innovation (Green et al., 2022; Hutchins et al., 1999). We contribute to this literature

in three key ways. First, we provide causal, large-scale evidence of how financial incentives shape representation in R&D. Our paper is related to Michelman and Msall (2022), who show that removing the FDA's guidance against inclusion of women of child-bearing potential in clinical trials increases the number of female-specific patents. However, Michelman and Msall (2022) find no effects of the FDA policy on female-focused clinical trials and do not observe enrollment criteria. Our results suggest that financial incentives may be more salient than regulatory guidance. Another related paper (Gupta, 2022) shows that female-lead projects enroll more female participants, but does not investigate the causal effects of a policy on representation.

Second, we provide empirical evidence that representation in the R&D process matters for product adoption. In recent work, Aslan et al. (2022) provide survey evidence that representation affects utilization for one under-represented group (Black Americans). We extend and confirm that their findings are applicable in another setting using real-world prescription outcomes. Other related work has found that representation in inventors matters for project development. Koning, Samila and Ferguson (2020) and (2021) find that female inventors are more likely to innovate in areas that serve women's needs and Nielsen et al. (2017) find that female authors are likely to consider sex heterogeneity in academic publications. We focus on the effects of inputs to the innovation process rather than innovators.

Third, we shed new light on the role of insurance expansion in contributing to innovation. While previous studies have shown how insurance can influence pharmaceutical innovation by shifting expected demand (e.g., Blume-Kohout and Sood (2013)), to our knowledge, ours is the first to examine how expanding insurance coverage that affects key *inputs* to the R&D process can influence pharmaceutical innovation. In particular, we contribute to a literature outside of economics on the impact of the Medicare Memorandum of 2000. This literature is mixed and mainly based on anecdotal or cross-sectional evidence (Unger et al., 2006). Concerns about small sample sizes and unobservable factors have hindered a clear understanding of causality and the general applicability of these findings. In contrast, we provide the first comprehensive, econometrically-based analysis of the memorandum.

Although our empirical analysis does not fully assess the overall welfare effects of the policy, the observed positive medium-term impact on key outcomes such as the number of trials, patient enrollment, and drug utilization suggest that that policies reducing financial barriers to patient enrollment could be effective mechanisms for increasing representation in clinical trials.

We proceed as follows. In Section 2, we discuss the institutional background. We describe our data in Section 3. Section 4 documents disparities in clinical research. Sections **??** and 6 present our main results. Finally, Section 7 concludes.

2 Institutional Background

2.1 Drug Development

Drug development typically begins with extensive pre-clinical laboratory research that involves testing a new drug candidate on animals and human cells. Once complete, the manufacturer begins the most expensive aspect of drug development: human testing of drugs in a series of clinical trials in which costs increase with each subsequent phase. Drugs that successfully demonstrate safety in Phase I trials proceed to Phase II trials in which their efficacy is tested in a few hundred participants. If successful, the drugs move to Phase III trials in which their efficacy is tested in several thousand participants. Upon successfully completing Phase III trials, the sponsor will submit a New Drug Application (NDA) to the FDA for final approval.

2.2 Costs of Clinical Research

The drug development process is costly (typically costing a manufacturer $800 million) and long (often taking between 8 and 12 years) (DiMasi, Hansen and Grabowski, 2003; DiMasi, Grabowski and Hansen, 2016). A key driver of these costs are patient recruitment and retention costs. Though costs vary across patient groups and diseases, estimates suggest average patient recruitment costs are $43,000 per patient (for Phase I) to $333,000 per patient (for Phase III) (Sertkaya et al., 2016). Manufacturers aim to enroll eligible participants as quickly as possible, since there are high fixed costs to keeping a trial open.[2]

These costs are often shared between manufacturers and participants (Pear, 2000). Manufacturers typically cover costs beyond routine clinical trial expenses, such as data analysis and other related costs. Participants, on the other hand, usually receive treatments without any or with minimal cost, but they may need to bear the costs linked to routine care, screening, and travel. Insurers often argue that clinical trial treatments are experimental and therefore do not cover the routine clinical trial expenses for participants. There is much uncertainty about who actually pays for specific components of clinical trials, which often deters people from participating or leads to thousands of dollars of unexpected expenses for people who join the trials (Pear, 2000).

[2]Source: Authors' own interviews with Boston clinical trial managers.

2.3 Inclusion of Older Adults In Clinical Trials

Older adults may be under-represented in clinical trials due to commodities, health literacy, limitations of decision making with cognitively impaired patients, and clinical trial costs (Herrera et al., 2010). Examples of these concerns include hearing difficulties that interfere with telephone interviews or physical immobility that affects transportation to the trial. Clinical trial locations are often set in urban hospitals, while older adults are more likely to live in rural locations than younger adults.

Pharmacokinetic differences and physiological age were also cited as important factors limiting the inclusion of older adults in clinical trials. Most trials exclude participants with some comorbidities, and older adults are more likely to have disqualifying health conditions. Older adults are also less likely to be willing to accept treatments with side-effects such as nausea or fatigue (Lara et al., 2001). A homogeneous trial population decreases the variance of treatment effects and therefore the sample size needed to have a certain amount of statistical power. Including older adults may therefore add additional costly variability. In addition to these concerns, Medicare did not cover the routine costs of clinical trials until the executive memorandum of 2000.

2.4 Medicare Memorandum of 2000

In June of 2000, President Clinton ordered Medicare to start covering most of the costs of clinical trials. The memorandum stated "Medicare will immediately begin to reimburse for the routine patient care costs, and costs due to medical complications associated with participation in a clinical trial." The sponsors of clinical trials would continue to pay for the analysis of data and other costs beyond the costs of routine care. This was enforced via an executive memorandum. White house officials stated a motivation for the change was to increase the number of elderly people who participate in clinical trials. Vice President Al Gore, speaking about the memorandum, said "Speeding up enrollment can accelerate the discovery and use of cost-saving, life-saving, new therapies" (Pear, 2000).

The stature in place before the Medicare Memorandum of 2000 was widely interpreted to bar reimbursement for the routine medical care that beneficiaries need when they participate in clinical trials. Many private insurers also historically did not cover these costs. These routine costs account for the bulk of the cost of most clinical trials. This memorandum also included an informational campaign to inform Medicare beneficiaries, doctors, hospitals, and other health care providers of the new policy.

3 Data

To understand the impact of lowering financial frictions on the development of medical innovations, we are interested in measuring how the Medicare Memorandum of 2000 shifted clinical trial enrollment at the disease level. A disease is defined by the International Classification of Diseases, version 9 (ICD-9) code. We use Medical Expenditure Panel Survey to identify diseases associated Medicare beneficiaries before 2000. We then investigate the relationship between disease-level exposure to the Medicare Memorandum of 2000 with the number of clinical trials, enrollment criteria, enrollment counts, and drug utilization. The data underlying these analyses are summarized below.

1. **High Elderly Share Diseases:** Following a commonly used approach (e.g., Duggan and Morton (2010), Blume-Kohout and Sood (2013), Acemoglu et al. (2006), and Krieger, Li and Papanikolaou (2022)), we estimate the share of individuals covered by Medicare associated with each ICD9 by using the 1996 to 1999 Medicare Expenditure Panel Survey (MEPS), a nationally representative survey of the U.S. civilian non-institutionalized population. Using data from the Full Year Consolidated Data File, we categorize diseases as having a "High Medicare Share" if they have an above the median share of Medicare individuals with that diagnosis (see Appendix Figure A.1).[3] As an example of Medicare shares among diseases, attention-deficit/hyperactivity disorder (ADHD) has a 3 percent Medicare share and the common cold has a 8 percent Medicare share. Both are classified as low Medicare share diseases. In contrast, vitamin D deficiency (54 percent Medicare share) and Parkinson's disease (81 percent Medicare share) both are high Medicare share diseases.

2. **Clinical Trials:** To create a dataset of clinical trials and enrollment, we begin with the data on clinical trials from the Cortellis Clinical Trials Intelligence Database ("Cortellis"). Cortellis contains clinical trial data from clinical trial registry websites, press releases, financial filings, and FDA submissions. This dataset contains each trial's enrollment criteria, start year, duration, phase, and associated ICD-9 code. We link this data on clinical trial enrollment characteristics that we obtain directly from ClinicalTrials.gov (see Appendix Figure A.2). This results in a dataset of 100,552 trial-diseases, and 10,058 trial-diseases with discrete age enrollment information.

3. **Drug Utilization:** To analyze how drug utilization shifts among diseases with a High Medicare Share, we collect data on drug utilization from the 1996 to 2010 MEPS

[3]For simplicity, we focus on categorizing diseases into two categories: high vs. low Medicare Share. However, our results are robust to using a continuous measure as in Appendix Figure A.3

Prescribed Medicines file. To isolate how the Medicare Memorandum of 2000 shifts drug utilization among the elderly, we further categorize drug utilization from three categories of individuals: aged 65+, 64 and below, and 55 and below.

4. **Disease Burden:** To determine under and over-representation within a diseases, we compute each ICD9's average disease burden by incorporating data from The Global Burden of Disease (GBD) dataset. We compute the disease burden among the elderly, as well as other demographics.

Throughout the paper, our unit of analysis is a narrowly defined disease category, as measured by the International Classification of Disease codes (ICD9). Our final dataset consists of 424 ICD9 codes. Appendix Table A.1 shows summary statistics at the disease-year level.

4 Documenting Disparities in Clinical Research

Using clinical trial and disease burden data from 1995 to 1999 (the last year before the Medicare Memorandum of 2000), we examine age disparities in clinical trial enrollment relative to the disease burden. For each ICD9 code, we calculate both the share of elderly participants in clinical trials for those diseases and the share of the disease burden that affects the elderly.

Figure 1 compares trial enrollment and disease burden at the ICD9-level. With a few exceptions (e.g., rheumatoid arthritis), the majority (79 percent) of diseases show a significantly smaller share of elderly participants in clinical trials relative to the actual share of elderly participants affected by that disease. These disparities are not limited to the elderly: while this paper focuses on age-based disparities, we also find historical under-representation of women in 74 percent of diseases and substantial shares of both over- and under-representation of black individuals (see Appendix Figure A.4).

Building on these insights, we investigate how the memorandum, which may have lowered financial frictions for patient enrollment, may have affected the elderly trial participation. We begin by exploring how the memorandum shaped the number of clinical trials initiated in elderly diseases and the inclusion of elderly participants in those trials. We then explore how changes in trial participant representation shaped drug utilization.

5 The Impact of the Medicare Memorandum on Clinical Trials

5.1 Empirical Strategy

We begin by empirically examining the role of the Medicare Memorandum of 2000 on elderly representation within clinical trials. Our baseline difference-in-differences (DID) specification compares outcomes in ICD9 codes with an above median share of elderly participants versus a below median share of elderly participants, before and after the Medicare Memorandum of 2000 change:

$$y_{jt} = \sum_t \beta_t \mathbf{1}\{year = t\} \times HighMcareShare_j + HighMcareShare_j + \gamma_{jt}\delta_{c(j)} + \delta_j + \delta_t + \epsilon_{jt} \tag{1}$$

where j is ICD9 disease code and t refers to calendar years. The outcome y_{jt} presents trial counts or trial enrollment counts within a disease and year. Due to the skewed nature of these measures, we take logs of the outcome data. The coefficient $HighMcareShare_j$ is an indicator for whether ICD9 disease code has an above median share of Medicare patients. The first terms on the right-hand side are the DID terms of interest, interactions of a full set of year dummies (excluding 2000) with the $HighMcareShare_j$. The regression also includes controls for whether the ICD9 code has an above median share of Medicare patients prior to 2000, ICD9 fixed effects (δ_j), and the year fixed effects (δ_t). To account for time-varying differences across disease markets (e.g., research costs, scientific opportunities), we include interactions of linear year with disease chapter (e.g., neoplasms) ($\delta_{c(j)}$). Standard errors are clustered at the ICD9 level.

For the set of coefficients, β_t, to represent the causal impact of the memorandum on clinical trials, ICD9 disease codes with high and low shares of Medicare patients must have evolved similarly in the absence of the memorandum. While we test this directly by an examination of parallel pre-trends, our identification could be threatened if other changes that directly affected Medicare patients occurred after the memorandum. For example, Blume-Kohout and Sood (2013) have documented that the introduction of Medicare Part D in 2006 led to shifts in R&D directed towards those patients, suggesting that Medicare Part D have shifted expected demand among Medicare patients. We discuss these possibilities and the robustness of our results to these factors at the end of Section 5.2.

Before proceeding to our causal estimates, descriptive evidence provides support for our

empirical strategy. Appendix Figure A.5 plots the total number of trials within the top 10 percent, 10-20 percent, etc. of diseases by share of Medicare patients. The number of trials per disease category is roughly parallel before 2000, but diseases with high shares of old diagnoses have many more trials afterwards.

5.2 Impact on the Rate of Clinical Trials

To understand how the memorandum shaped research, we begin by exploring whether the memorandum changed the level of research in clinical trials in diseases common among the elderly. Figure 2 shows that prior to 2000, the difference in the number of clinical trials between diseases with high vs. low Medicare shares prior to 2000 is statistically indistinguishable from zero. This lack of a pre-existing trend offers support for our DID strategy. In contrast, after the memorandum, we observe a substantial increase in the relative number of clinical trials in diseases with a high vs. low Medicare shares prior to 2000. This increase remains large, positive, and statistically significant for the next seven years. Estimates in Table 1 reveal that the memorandum is associated with a 20 percent relative increase in the number of clinical trials in diseases with high Medicare share prior to 2000 in each year after the memorandum. This is an economically meaningful increase, with an additional clinical trial being conducted in a given disease each year following the introduction of the memorandum.

In addition, we conduct a variety of robustness checks. One concern is that research within diseases with a high Medicare shares prior to 2000 may have been evolving on different trends, for reasons unrelated to the memorandum. As indicated earlier, the Medicare Modernization Act was signed in December of 2003, and before Medicare Part D coverage went into effect in 2006. Though Figure 2 shows that the increase in trials in diseases with above median elderly diagnoses occurs several years before 2003, we conduct two robustness tests to ensure that our results are not driven by the introduction of Part D. First, in Column 1 of Appendix Table A.2, we show that our results are robust to restricting the sample years to 1995 to 2003. Second, we show that are results are robust to providing an additional control for Medicare Part D. Column 1 of Appendix Table A.3 shows that in a horse-race between the memorandum and Part D, the memorandum has a meaningful impact on the number of total clinical trials. Additionally, our results are robust to examining the total number of trials (see Appendix Figure A.6), to looking at individual trial phases (see Appendix Figure A.7), and to using an alternative, continuous measure of exposure to the memorandum (see Appendix Figure A.3).

5.3 Impact on Clinical Trial Representation

While the previous results suggests that the memorandum increased the number of clinical trials in affected diseases, the results need not indicate that the memorandum led an increase in the enrollment of elderly participants in these trials. In the extreme, the memorandum might have led to a disproportionate increase in non-elderly participants enrolled in trials for diseases with a high Medicare share. This could further worsen the underrepresentation disparities in clinical trial research. To address these concerns, we document evidence that memorandum shifted trial sponsors' clinical trial recruitment decisions and increased in the quantity of the elderly participants enrolled within each trial.

Panel A of Figure 3 examines the impact of the memorandum on trial recruitment efforts. A clinical trial has enrollment criteria which list the types of participants who can volunteer for a trial.[4] A trial is categorized as recruiting any elderly participants if the enrollment criteria include any adults at age 65 or over. We focus on enrollment patterns for trials that include elderly participants in their enrollment criteria. This may include trials that include only the elderly participants and those that include both elderly and non-elderly participants. We compare these trials against those whose enrollment criteria include only non-elderly participants. Panel A of Figure 3 presents results the estimation of equation 1 that shows that greater exposure to the memorandum is associated with an immediate and sustained increase in the relative number of trials enrolling any elderly participants.

Seemingly unrelated regressions, which permits a direct comparison of coefficients, are presented in Columns 2 and 3 of Table 1. The estimates indicate that, among affected diseases, there was a 26 percent yearly increase in the number of trials recruiting any elderly participants; in contrast, we find no significant effect of the memorandum on trials recruiting non-elderly participants.[5] These results suggests that the increase in trials following the memorandum consisted largely of trials targeting the enrollment of elderly participants.

To examine whether the shift in trial recruitment also translated to an increase in the *actual* number of elderly participants enrolled in each trial, we next examine how patient enrollment within a trial evolved following the policy. Panel B of Figure 3 and Columns (3) and (4) Table 1 shows the policy's effect on the enrollment of elderly vs. non-elderly participants per trial. The results suggest that the number of elderly participants enrolled increases by

[4]Examples of enrollment criteria include "Female", "Ages 18-44", "Type 2 diabetes", and "ability to walk 30 m independently."

[5]Appendix Figure A.8 restricts the sample to trials for which the enrollment criteria includes *only* elderly participants or *only* non-elderly participants. This sample includes only 14 percent of our sample, since most trials enroll broad ages. This figure shows a more significant increase in elderly enrollment criteria right after the Medicare policy and a corresponding decrease in the number of trials that only enroll non-elderly participants.

nearly 60 percent. Notably, the increase in the number of non-elderly participants also increases and is not statistically significantly different. These trends correspond to a shift in age disparities in clinical research: Appendix Figure A.9 presents a prepost analysis that reveals a general decline in age disparities in clinical trial enrollment relative to the disease burden after 2000.

Taken together, these findings hint broader effects of the memorandum on trial enrollment. The results are consistent with the view that the memorandum lowered the expected costs of enrolling elderly participants. As a results, firms responded by conducting larger clinical trials. This expansion in trial size did not occur at the expense of other age groups; though firms expanded trial enrollment criteria to include the elderly, firms successfully increased the enrollment of both elderly and non-elderly participants.

6 The Impact of Medicare Memorandum on Drug Utilization

A recent literature highlights that increases in representation in the R&D process may influence product utilization. In this section, we explore how representation shapes drug utilization. The results of clinical trials are often used as marketing materials by pharmaceutical firms and firms may highlight increased representation or efficacy of a drug among elderly participants. Patient's physicians may hear about this new research from pharmaceutical representatives or their own research and may recommend products with recent representative evidence to elderly patients. For this analysis, we conduct an individual-year level analysis where we compare drug utilization among elderly versus middle-aged individuals, before and after the Medicare Memorandum of 2000 change. We regress

$$y_{it} = \sum_t \beta_t \mathbf{1}\left\{year = t\right\} \times Elderly_{k(i)} + Elderly_{k(i)} + \delta_t + \epsilon_{it} \tag{2}$$

where y_{it} is the number of unique prescriptions among ICD9 codes with either a high or low share of diagnoses among Medicare beneficiaries for individual i in year t. Age categories are denoted by $k(i)$ and $Elderly_{k(i)}$ refers to whether the individual is over 65, relative to a control group of individuals aged 45-54. The δ_t refer to calendar year fixed effects. Standard errors are robust.

Figure 4 shows that following memorandum, we observe a substantial increase in the use of elderly-oriented drugs among elderly patients, compared with both drugs targeted towards younger diseases and drug utilization patterns among non-elderly patients. The findings are consistent with Alsan and Wanamaker (2017) which find that physicians are more likely to prescribe new drugs to those represented populations in clinical trials, and those patients

from the represented groups are more likely to use these treatments drugs.

In 1999, the average elderly individual took 2.2 unique prescriptions in elderly disease categories and 0.9 unique prescriptions in young disease categories.[6] The average individual aged 45-54 years took 1.0 unique prescriptions in elderly disease categories and 0.7 unique prescriptions in young disease categories. Therefore, the increase of 0.5 unique prescriptions for elderly individuals in elderly diseases represents a 23 percent increase over the base of 2.2 unique prescriptions in this category.

7 Discussion and Conclusion

Amid rising public pressure, policy makers are looking for ways to minimize demographic disparities in the innovation process. In this paper, we study how insurance policies aimed lowering financial frictions affect representation in drug development. Diseases that are more affected by the policy see a 17 percent increase in the number of clinical trials. Within these diseases, firms expanded their clinical trial enrollment criteria to include elderly patients. This resulted an in significant increase in both elderly patients and non-elderly patients. In addition, we observe a significant increase in drug utilization among the elderly, suggesting that the Medicare-driven shift in representation could have a meaningful shift in drug utilization.

Our results have at least three important insights that future research could extend. First, our analysis identifies a relative increase in clinical trial activity, elderly patient enrollment criteria, and drug utilization among diseases with high vs. low levels of exposure to the Medicare Memorandum of 2000. To quantify the true welfare costs of the memorandum, it is necessary to distinguish whether this comes from an overall increase in innovative activity and drug utilization in affected diseases, or a reallocation of research activity and drug utilization from less to more affected diseases. Second, our findings largely speak to representation at the trial-level, which is important as it allows us to more precisely examine how the memorandum shaped clinical trial activity. However, firms typically conduct a set of clinical trials to support an individual new drug approval. Future work should characterize how the Medicare Memorandum of 2000 shapes representation at drug-level. Third, our findings largely speak to the short-term implications of representation on drug utilization. A more direct analysis into how increases in representation might shape the underlying quality of evidence generated (e.g., are estimates less precise?) is an important topic for future research.

From a public policy standpoint, our results on age-concordance can offer valuable insights into how policies might improve concordance on other demographic dimensions. For

[6]The average elderly individual took 5.1 unique prescriptions, but not all prescriptions could be assigned to a disease with a Medicare share.

instance, low-income individuals are under-represented in clinical trials. However, in January 2022, Medicaid began to cover routine costs for its recipients participating in clinical trials (Takvorian, Guerra and Schpero, 2021). Our work suggests this policy may meaningfully improve representation of low income individuals in the pharmaceutical innovation process.

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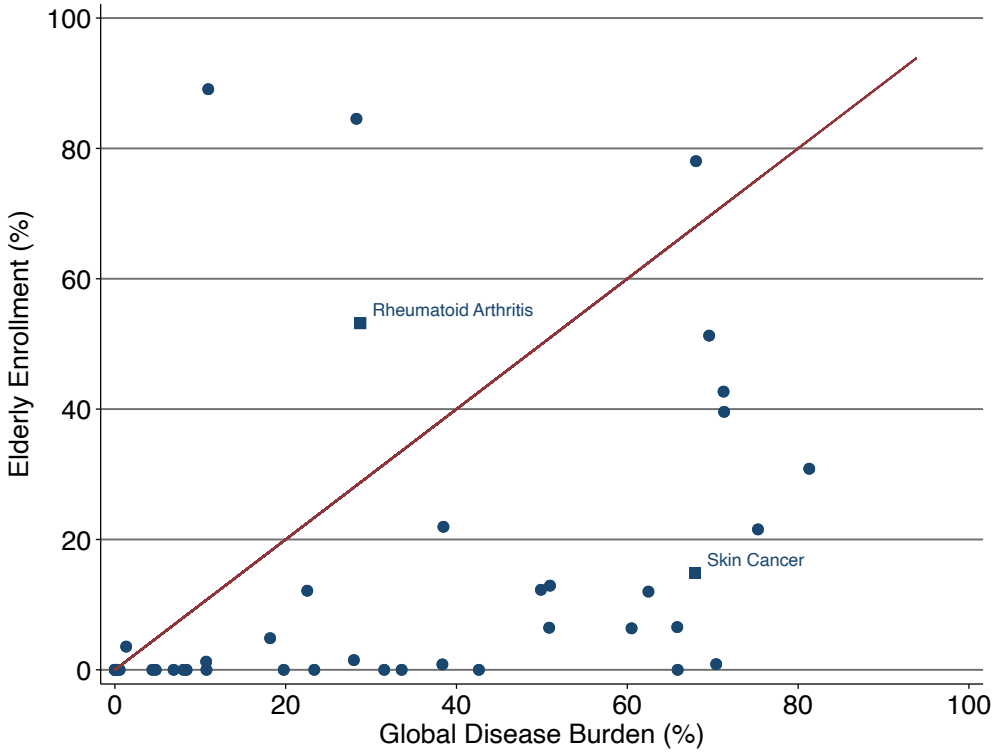
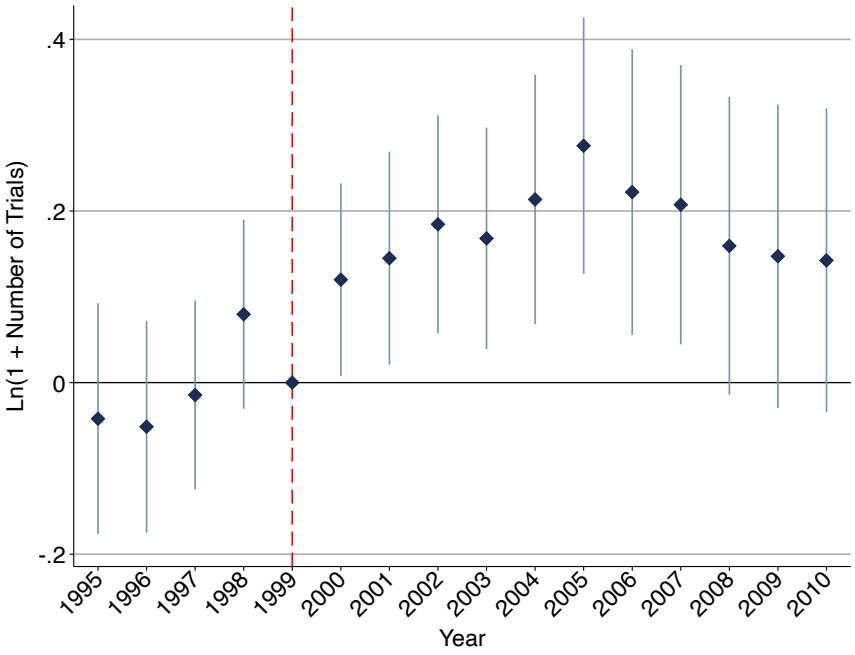
Figures and Tables

Figure 1: Disparities in Elderly Trial Enrollment, 1995-1999



Note: Each point represents an ICD9 code, with the x-axis showing the share of the global disease burden among the elderly (aged 65+) and the y-axis presenting the average share of elderly participants enrolled in clinical trials for those diseases, between 1995-1999. The 45-degree line represents perfect parity between disease burden and trial enrollments. Points below this line indicate diseases where disease burden exceeds elderly trial enrollment.

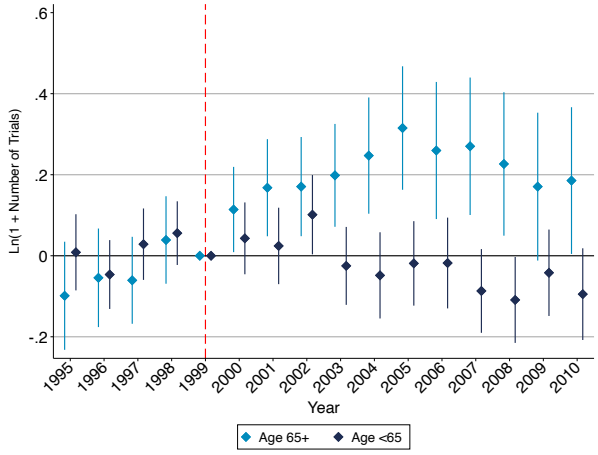
Figure 2: Impact of Medicare Reimbursement Expansion on Ln Total Number of Trials: Event Study



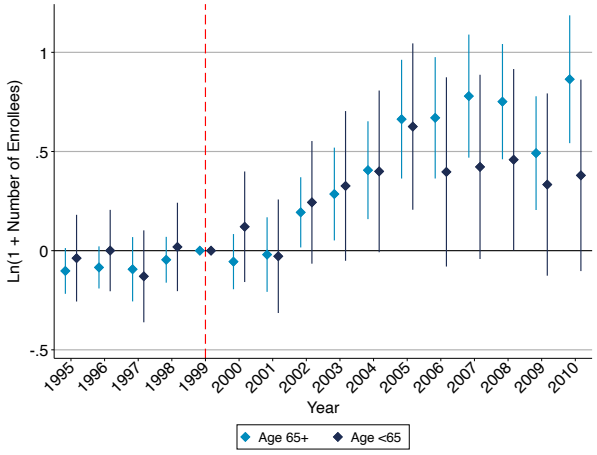
Note: Figure presents event study coefficients from the estimation of equation 1. We plot the coefficients on the interaction between year and an indicator for whether a disease had above median share of diagnoses among the elderly from 1996-1999. An observation is a disease and year and the outcome is the natural log of the number of trials in a disease year.

Figure 3: Impact of Medicare Reimbursement Expansion: Mechanisms

(a) Trials, by Enrollment Criteria

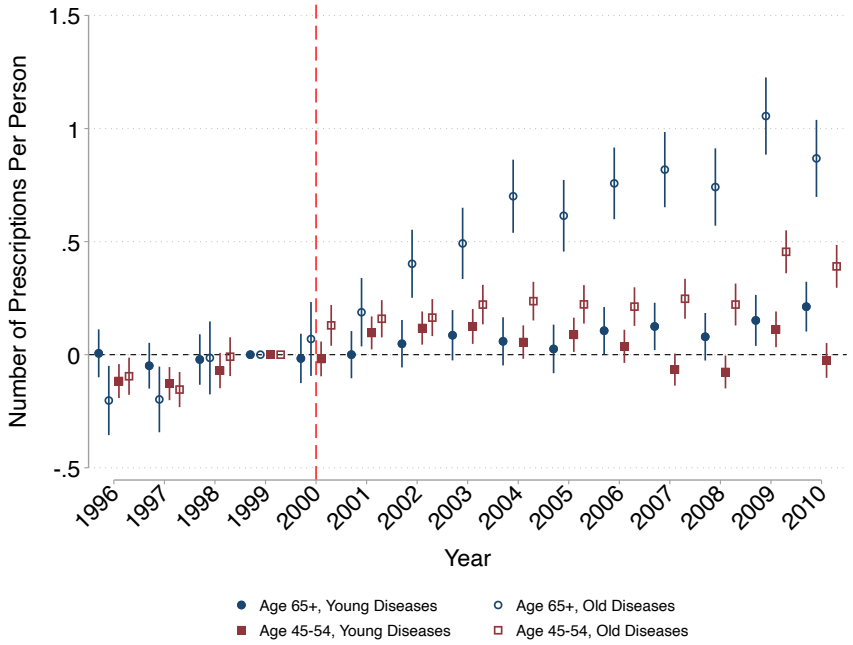


(b) Number of Participants Enrolled



Note: Figure presents event study coefficients from the estimation of equation 1. We plot the coefficients on the interaction between year and an indicator for whether a disease had above median share of diagnoses among the elderly from 1996-1999. An observation is a disease and year. Panel (a) presents estimates using two outcomes: (1) the natural log of the number of trials that include elderly participants and (2) the natural log of the number of trials that do not include elderly participants in their enrollment criteria. All trials are in one of these two categories. Panel (b) presents coefficients from two different regressions. In one the outcome is the natural log of the number of participants who are elderly ("Age 65"); in another the outcome is the natural log of other participants with a non-elderly age ("Age <65").

Figure 4: Prescriptions by Age and Disease Category



Note: Figure presents event study coefficients from the estimation of equation 2. In the coefficients labeled "Age 65+", we plot the coefficients on the interaction between an indicator for whether the individual is above 65 and year. In the coefficients labeled "Age 45-54", we plot the coefficients on the interaction between an indicator for whether the individual is 45-54 and year. The outcome is either the number of unique prescriptions per person in diseases with an above median share of diagnoses among the elderly ("Old diseases"), or a below median share of diagnoses among the elderly ("Young Diseases").

Table 1: Impact of Medicare Reimbursement Expansion

	Total Trials Ln(1 + # Trials)	Enrollment Criteria Ln(1 + # Trials)		Actual Enrollment Ln(1 + # Patients)	
		Only Age < 65	Any Age ≥ 65	Age < 65	Age ≥ 65
	(1)	(2)	(3)	(4)	(5)
Post × MedicareShare	0.184**	-0.0249	0.241***	0.342**	0.465***
	(0.0575)	(0.0277)	(0.0608)	(0.124)	(0.0728)
Post	-0.0676	0.0931***	-0.117**	-0.243**	-0.354***
	(0.0360)	(0.0222)	(0.0357)	(0.0871)	(0.0518)
Mean of Dep. Var.	0.921	0.290	0.824	1.055	0.483
Wald Test P-value		0.00		0.16	
Observations	6448	6448	6448	6448	6448
Adjusted R^2	0.815	0.586	0.801	0.429	0.359

Note: Table presents coefficients from regressing the outcome in each column on an indicator for after the Medicare Memorandum of 2000 ("Post"), an indicator for whether a disease has an above median share of diagnoses among the elderly ("Medicare Share"), and the interaction between the two. We control for ICD-9 fixed effects (which encompass the "Medicare Share" indicator), the year of the trial, and the ICD-9 category by year trends. The "Wald Test P-value" is the p-value comparing the $Post \times MedicareShare$ coefficient in (2) vs. (3) and (4) vs. (5). Column (1) estimated using OLS. Columns (2)-(5) estimated using seemingly unrelated regressions.

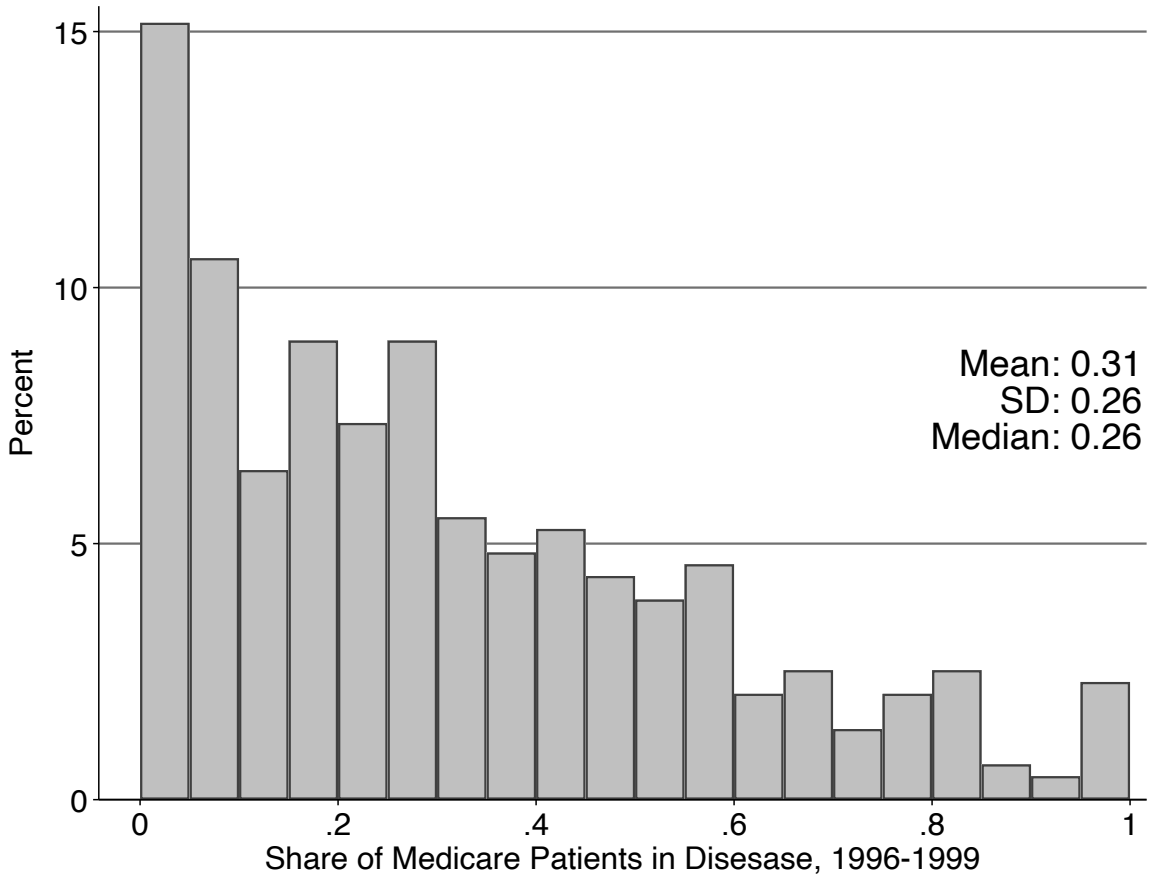
A Appendix

Appendix A: Data Construction

Identifying High Medicare Share Diseases

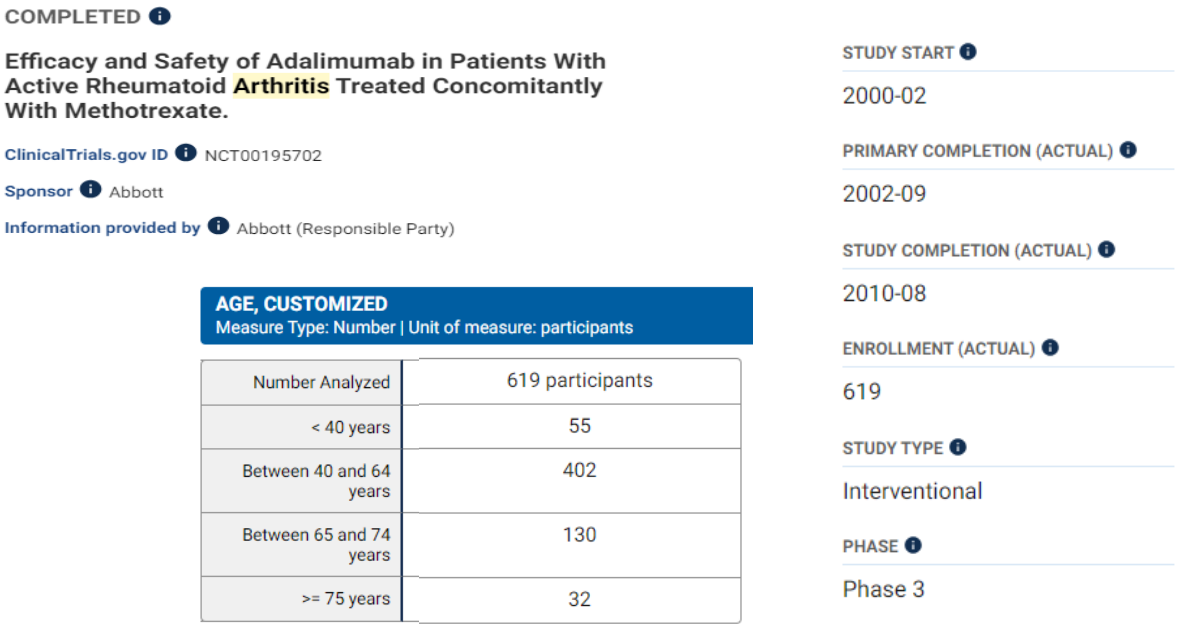
Clinical Trial Enrollment Data

Figure A.1: Disease-Level Exposure to Medicare Policy



Note: Figure plots the share of diagnoses in a disease among Medicare patients. The sample used is the MEPS from 1996-1999.

Figure A.2: Clinical Trial Enrollment Data from ClinicalTrials.gov



COMPLETED

Efficacy and Safety of Adalimumab in Patients With Active Rheumatoid Arthritis Treated Concomitantly With Methotrexate.

ClinicalTrials.gov ID NCT00195702

Sponsor Abbott

Information provided by Abbott (Responsible Party)

AGE, CUSTOMIZED
Measure Type: Number | Unit of measure: participants

Number Analyzed	619 participants
< 40 years	55
Between 40 and 64 years	402
Between 65 and 74 years	130
>= 75 years	32

STUDY START
2000-02

PRIMARY COMPLETION (ACTUAL)
2002-09

STUDY COMPLETION (ACTUAL)
2010-08

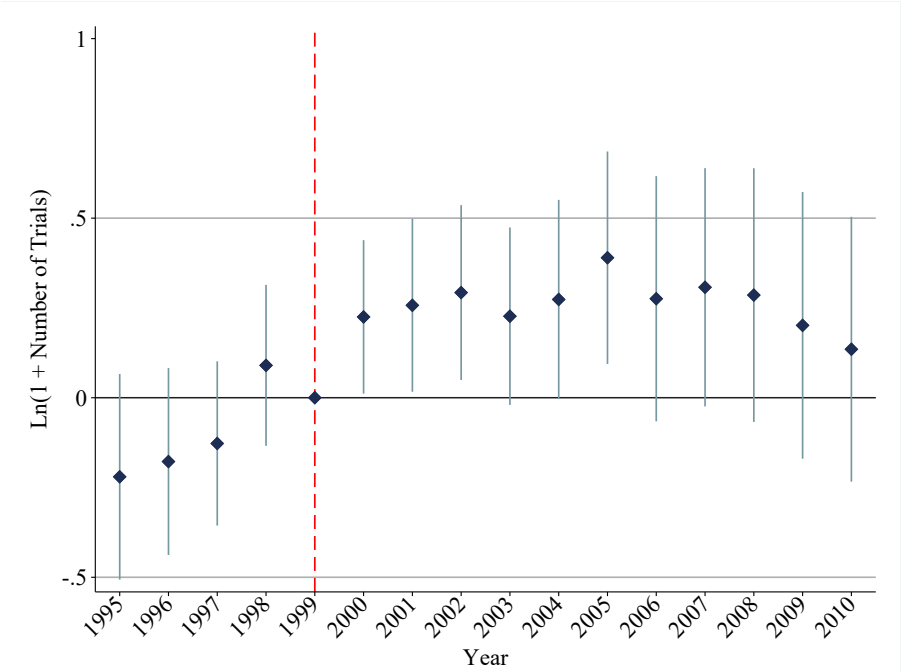
ENROLLMENT (ACTUAL)
619

STUDY TYPE
Interventional

PHASE
Phase 3

Note: Figure shows an example of trial enrollment counts in ClinicalTrials.gov. This trial was a phase 3 trial testing the efficacy of adalimumab. The trial was conducted in 2000, and adalimumab (brand name Humira) was approved by the FDA in 2002. This trial enrolled 130 individuals aged 65-74 years and 32 individuals aged 75+ years, for a total of 162 elderly participants out of 619 total enrolled.

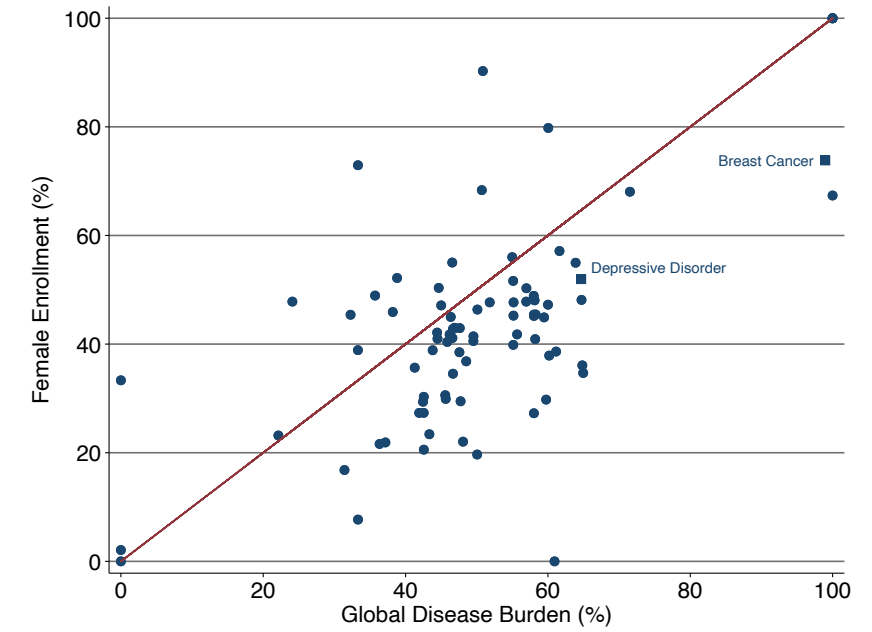
Figure A.3: Impact of Medicare Memorandum using Continuous Medicare Share



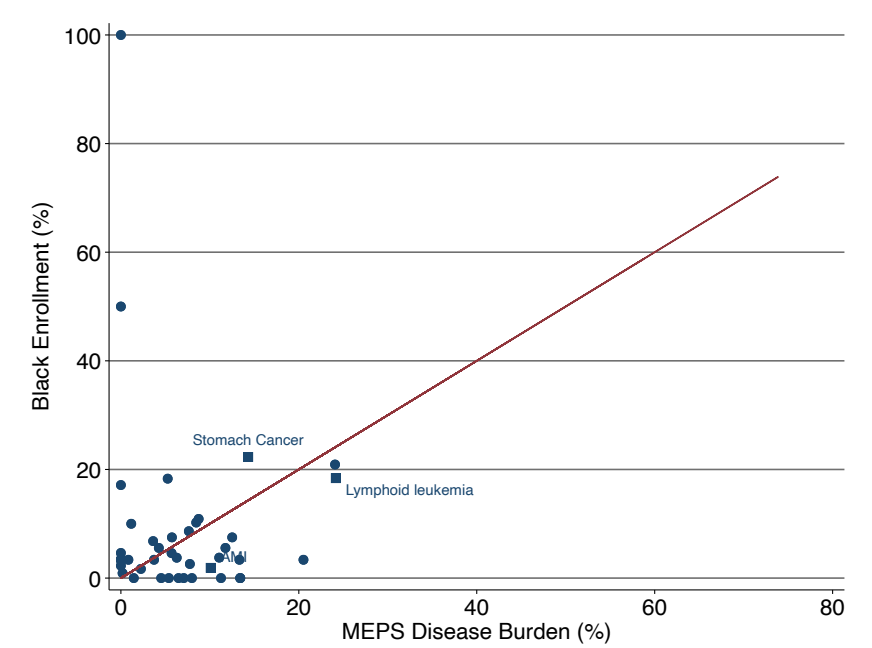
Note: Figure is similar to Figure **??**= * uses a continuous rather than binary measure of Medicare share of diagnoses. We plot the coefficients on the interaction between year and a continuous measure of the share of diagnoses among Medicare patients from 1996-1999. An observation is a disease and year and the outcome is the natural log of the number of trials in a disease year.

Figure A.4: Disparities in Trial Enrollment, 1995-1999

(a) Gender

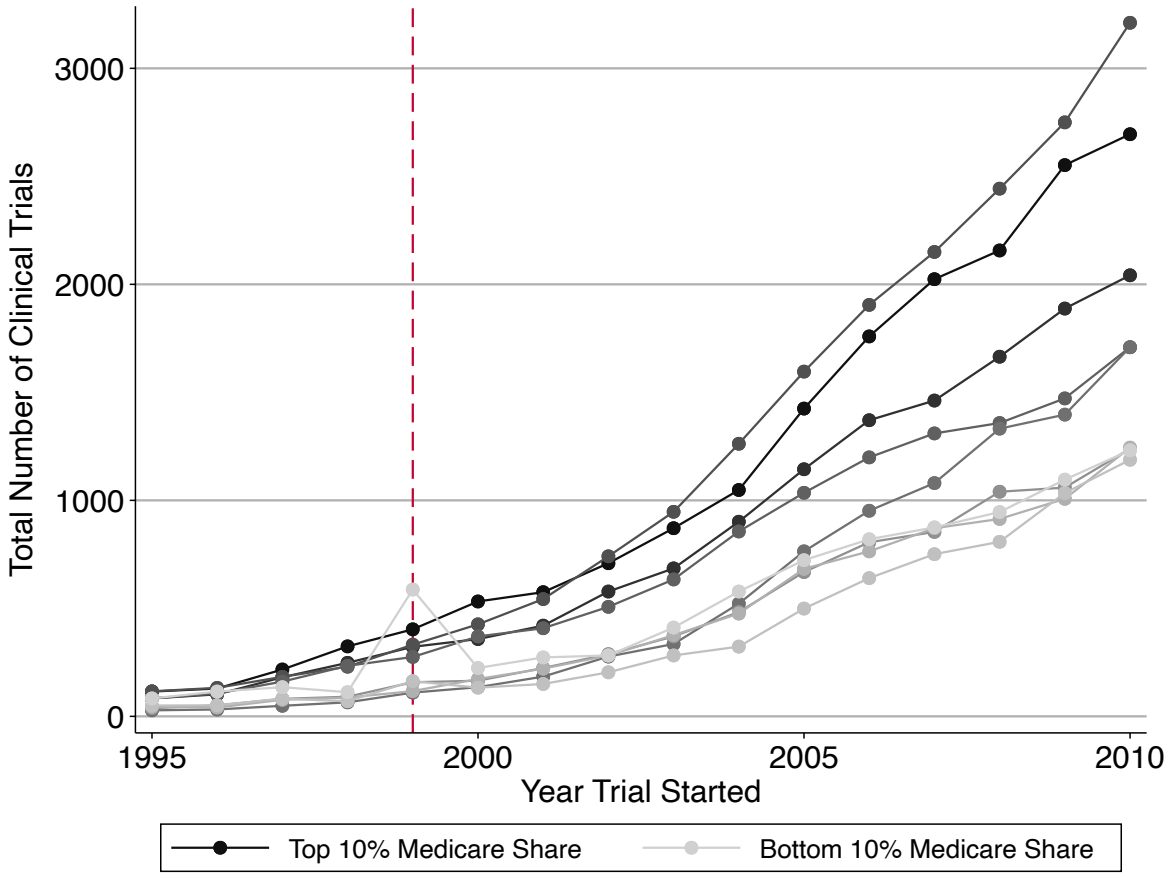


(b) Race



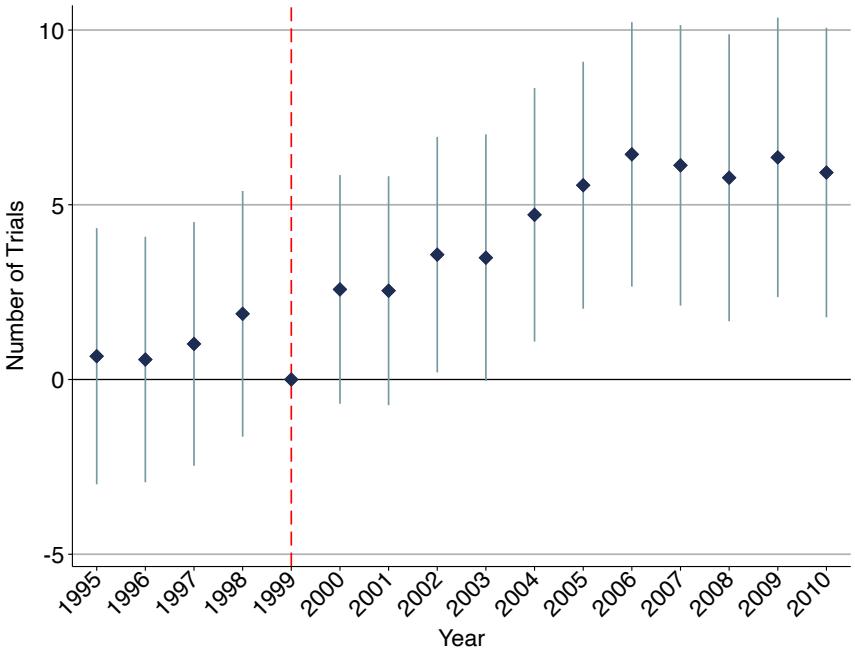
Note: Each point represents an ICD9 code, with the x-axis showing the share of disease burden among women (panel a) or black individuals (panel b). The y-axis presents the average enrollment among women (panel a) or black individuals (panel b) in clinical trials for those diseases, between 1995-1999. The 45-degree line represents perfect parity between disease burden and trial enrollments. Points below this line indicate diseases where disease burden exceeds trial enrollment.

Figure A.5: Descriptive Evidence of Medicare Policy



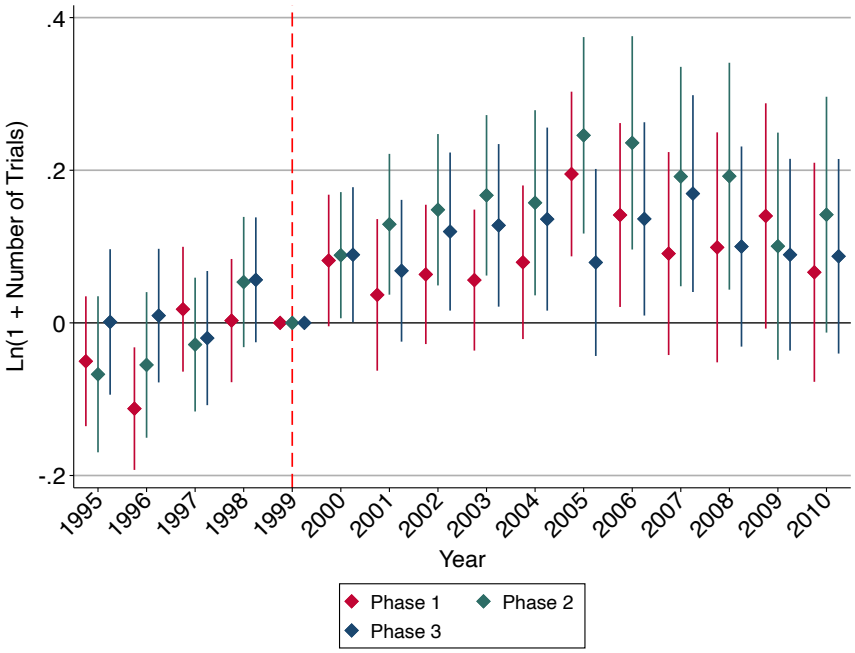
Note: Figure plots the total number of clinical trials within disease categories. The darkest line refers to diseases in the top 10 percent of Medicare share of diagnoses. The second-darkest contains the diseases in the top 10-20 percent of Medicare share of diagnoses all the way down to the lightest line which contains the lowest 10 percent of diseases in terms of the Medicare share of diagnoses.

Figure A.6: Impact of Medicare Memorandum on Total Number of Trials: Event Study



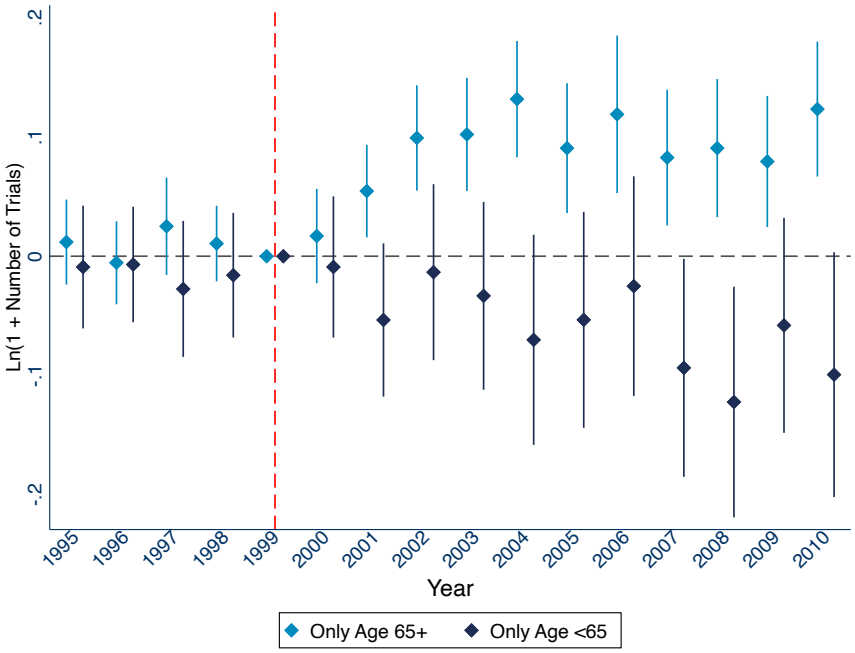
Note: Figure presents event study coefficients from the estimation of equation 1. We plot the coefficients on the interaction between year and an indicator for whether a disease had above median share of diagnoses among the elderly from 1996-1999. An observation is a disease and year and the outcome is the number of trials in a disease year.

Figure A.7: Impact of Medicare Reimbursement Expansion on Total Number of Trials, by Trial Phase)



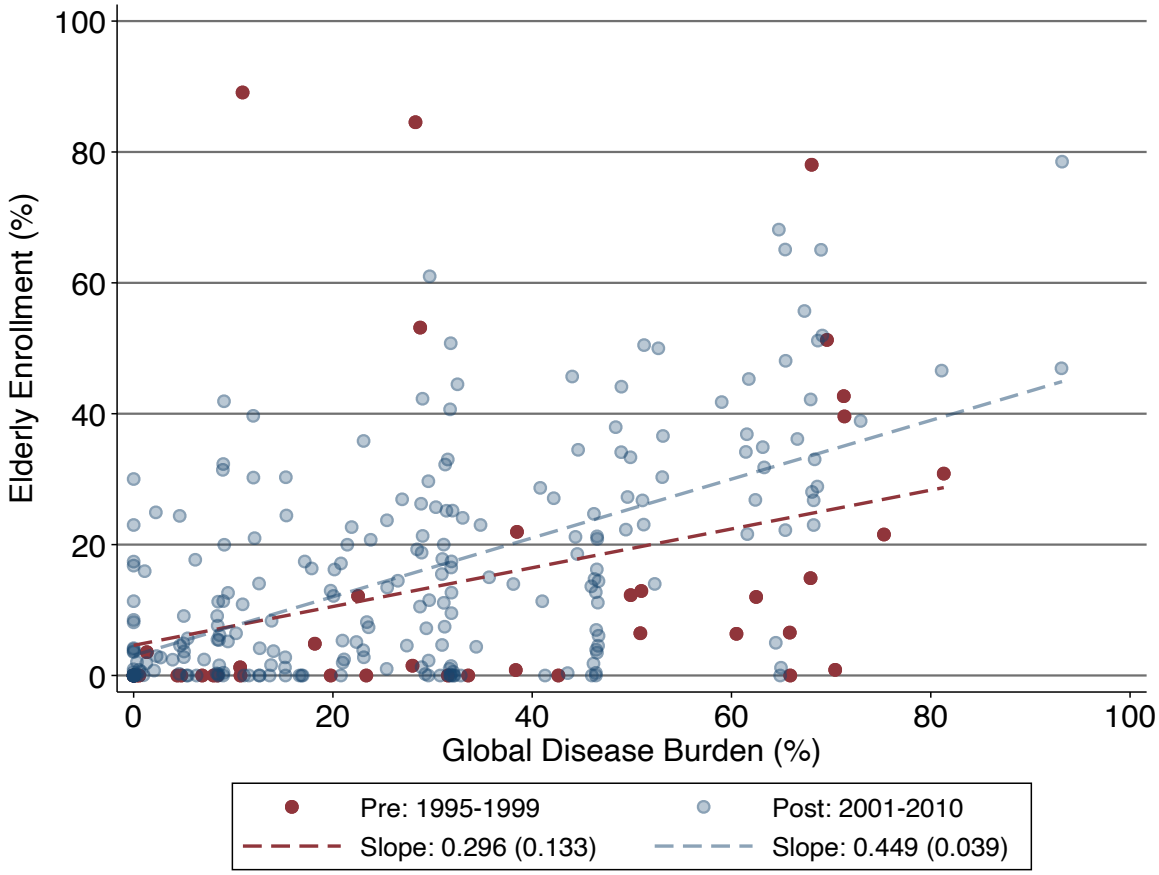
Note: Figure presents event study coefficients from the estimation of equation 1. We plot the coefficients on the interaction between year and an indicator for whether a disease had above median share of diagnoses among the elderly from 1996-1999. An observation is a disease and year. The outcomes are the natural log of the number of Phase 1 trials, the natural log of the number of Phase 2 trials, and the natural log of the number of Phase 3 trials.

Figure A.8: Trials, by Enrollment Criteria



Note: Figure presents event study coefficients from the estimation of equation 1. We plot the coefficients on the interaction between year and an indicator for whether a disease had above median share of diagnoses among the elderly from 1996-1999. An observation is a disease and year. This figure presents results using two outcomes: (1) the natural log of the number of trials that *only* include elderly participants, not participants below age 65 and (2) the natural log of the number of trials *only* include participants below 65 in their enrollment criteria. This figure includes a subset of the data from Figure 3.

Figure A.9: Disparities in Elderly Enrollment Over Time



Note: Each point represents an ICD9 code, with the x-axis showing the share of disease burden among the elderly (aged 65+) and the y-axis presenting the average share of elderly participants in clinical trials for those diseases. The maroon dots average across 1995-1999 while the navy dots average across 2001-2010. These two lines have statistically different slopes with P<0.001. The 45-degree line represents perfect parity between disease burden and trial enrollments.

Table A.1: Summary Statistics

	Count (1)	Mean (2)	Median (3)	SD (4)	Min (5)	Max (6)
A. Disease-Year Level						
Medicare Share	6784	0.31	0.26	0	0	1
# Trials: Total	6784	5.20	1.00	14	0	363
# Trials: Criteria Only Age < 65	6784	0.65	0.00	2	0	27
# Trials: Criteria Any Age ≥ 65	6784	4.55	0.00	13	0	336
# Patients Per Trial: Age < 65	6784	61.50	0.00	1055	0	82225
# Patients Per Trial: Age ≥ 65	6784	25.55	0.00	301	0	7932
B. Patient-Year Level						
# Prescriptions: Low Medicare Share Diseases	112910	0.83	0.00	1	0	19
# Prescriptions: Higher Medicare Share Diseases	112910	1.98	1.00	2	0	20

Note: Table presents summary statistics for outcomes at the disease-year level (Panel A), or the patient-year level (Panel B). Medicare share is the share of diagnoses in that disease among Medicare patients. "Criteria Any Age >= 65" includes the number of trials with enrollment criteria that include elderly individuals. "Criteria Only Age <65" includes the number of trials with enrollment criteria that do not include elderly individuals. "# of Prescriptions" refers to the number of unique prescriptions per person in that disease category in the MEPS.

Table A.2: Impact of Medicare Reimbursement Expansion (1995 to 2003)

	Total Trials Ln(1 + # Trials)	Enrollment Criteria Ln(1 + # Trials)		Actual Enrollment Ln(1 + # Patients)	
		Age < 65	Age ≥ 65	Age < 65	Age ≥ 65
	(1)	(2)	(3)	(4)	(5)
Post × MedicareShare	0.142**	0.0154	0.173***	0.143	0.119*
	(0.0459)	(0.0263)	(0.0458)	(0.102)	(0.0528)
Post	-0.174***	-0.0277	-0.178***	-0.0327	-0.0959*
	(0.0368)	(0.0255)	(0.0349)	(0.0784)	(0.0406)
Mean of dep. var.	0.619	0.242	0.519	0.391	0.160
Wald Test P-value			0.00		0.74
Observations	3627	3627	3627	3627	3627
Adjusted R^2	0.801	0.598	0.787	0.338	0.241

Note: Table presents coefficients from regressing the outcome in each column on an indicator for after the Medicare Memorandum of 2000 ("Post"), an indicator for whether a disease has an above median share of diagnoses among the elderly ("Medicare Share"), and the interaction between the two. We also include an indicator for after Medicare Part D was announced in 2003 ("PostPartD"), as well as interacted with Medicare Share. We control for ICD-9 fixed effects (which encompass the "Medicare Share" indicator), the year of the trial, and the ICD-9 category by year trends. The "Wald Test P-value" is the p-value comparing the $Post \times MedicareShare$ coefficient in (2) vs. (3) and (4) vs. (5). Column (1) estimated using OLS. Columns (2)-(5) estimated using seemingly unrelated regressions.

Table A.3: Comparison between Medicare Memorandum of 2000 and Medicare Part D

	Total Trials Ln(1 + # Trials)	Enrollment Criteria Ln(1 + # Trials)		Actual Enrollment Ln(1 + # Patients)	
		Only Age < 65	Any Age ≥ 65	Age < 65	Age ≥ 65
	(1)	(2)	(3)	(4)	(5)
Post2000 × MedicareShare	0.161***	0.0275	0.198***	0.195	0.159**
	(0.0455)	(0.0267)	(0.0459)	(0.104)	(0.0579)
Post2000	-0.0181	0.0621**	-0.0546	0.0446	-0.114**
	(0.0323)	(0.0221)	(0.0307)	(0.0816)	(0.0440)
PostPartD × MedicareShare	0.0420	-0.0945**	0.0769	0.266	0.551***
	(0.0467)	(0.0290)	(0.0497)	(0.136)	(0.0882)
PostPartD	0.106**	0.0336	0.0985**	0.583***	0.00369
	(0.0336)	(0.0220)	(0.0341)	(0.0998)	(0.0578)
Mean of dep. var.	0.921	0.290	0.824	1.055	0.483
Wald Test P-value		0.00		0.63	
ICD9 FEs	Yes	Yes	Yes	Yes	Yes
ICD9 × Year Trends	Yes	Yes	Yes	Yes	Yes
Observations	6448	6448	6448	6448	6448
Adjusted R^2	0.816	0.587	0.802	0.438	0.369

Note: Table presents coefficients from regressing the outcome in each column on an indicator for after the Medicare Memorandum of 2000 ("Post"), an indicator for whether a disease has an above median share of diagnoses among the elderly ("Medicare Share"), and the interaction between the two. We control for ICD-9 fixed effects (which encompass the "Medicare Share" indicator), the year of the trial, and the ICD-9 category by year trends. "Wald Test P-value" is the p-value comparing the $Post2000 \times MedicareShare$ coefficient in (2) vs. (3) and (4) vs. (5). Column (1) estimated using OLS. Columns (2)-(5) estimated using seemingly unrelated regressions.