Representation in Product Development: Evidence from Insurance and Clinical Trials*

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Abstract

We investigate the causes and consequences of demographic disparities in product development. We focus on how insurance policies affect elderly enrollment in clinical trials. In 2000, Medicare extended coverage for clinical trial costs. This policy shifted the rate and direction of clinical research, leading to an 18 percent increase in trials targeting diseases common among the elderly, compared to those affecting younger populations. We find trial sponsors expanded the enrollment criteria of trials to include more elderly participants. This policy was also associated with increase in drug utilization for elderly drugs.

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1 Introduction

During the research and development (R&D) process, firms must decide which users to engage with to develop, prototype, and test their products. Diverse representation in the R&D process may support the development of new products that effectively target these groups and spur their adoption.[1] However, increasing diversity in the R&D process may entail additional costs, complex logistics, and additional time to establish trust with different user groups. In this paper, we study how financial frictions shape user representation in R&D and examine how changes in representation subsequently impact product adoption.

We focus on drug development, where firms enroll participants in clinical trials to generate information about a drug's safety and efficacy. The information generated from clinical trials play an important role in shaping the decisions of regulators, physicians, and patients. In recent years, policymakers and researchers have increasingly called for the federal government to address the persistent underrepresentation of specific demographic groups—specifically, the elderly, women, and Black individuals—in clinical trials relative to the prevalence of the diseases affecting these groups. 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). While factors such as trust (Alsan and Wanamaker, 2017), stereotypes (Hebert, 2019), and safety concerns (Nadel, 1992) may contribute to participant disparities, financial barriers are frequently cited as a significant driver (Lara et al., 2001).

This paper investigates how expanding insurance coverage of clinical trials for elderly individuals affects 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).[2] 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 higher drug development costs.

[1] For simplicity, "representation" in the R&D process is defined as the extent to which the demographics of users involved in testing mirrors the composition of the eventual end-users of the product.

[2] See https://clintonwhitehouse3.archives.gov/WH/New/html/20000607.html.

Prior to 2000, there was widespread uncertainty about reimbursement of clinical trials by Medicare. Medicare, along with most private insurance plans, could exclude coverage of services in clinical trials on the basis that the treatment was experimental or investigational (U.S. General Accounting Office, 1999). Therefore, drug manufacturers or patients were often responsible for the high routine patient costs of qualifying clinical trials.

To examine the causal impact of the Medicare Memorandum of 2000 on drug development and adoption, we leverage a difference-in-differences (DID) design, utilizing cross-disease variation in exposure to the Medicare policy. In particular, we examine (1) the number of clinical trials targeting diseases commonly occurring among the elderly (individuals aged over 65), (2) the number of trials that broadened their enrollment criteria to include elderly participants and the actual number of elderly participants in these trials, and (3) the rate at which the elderly population adopts pharmaceutical treatments for diseases that are common among Medicare recipients. We assemble a new dataset of clinical trials spanning 1995 to 2010, including the trial start 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 drugs among the elderly and for drugs targeted at elderly diseases.

Our findings suggest that the Medicare Memorandum of 2000 meaningfully shifted drug development. We find that diseases most affected by the memorandum experienced an 18 percent increase in the number of clinical trials, relative to diseases that were least affected. Importantly, this increase 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. Additionally, our results are robust to both controlling for the passage of Part D and to excluding years after the passage of Part D.

To examine mechanisms, 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, among affected diseases, firms increased the number of clinical trials with patient enrollment criteria targeted towards the elderly 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 led to a 60 percent increase in the number of elderly participants per trial. We also document a 40 percent increase non-elderly trial participants, suggesting the presence of positive spillovers across the enrollment of different patient groups.

These findings are economically meaningful: in our setting, we observe an average of 5.2 trials within a disease in each year. Sertkaya et al. (2016) estimate that the average cost of a clinical trial is $12.3 million, suggesting that the 18 percent increase due to the Medicare Memorandum of 2000 spurred clinical investments of $11.6 million annually per disease common among the elderly. Importantly, these investments led to a significant increase in targeting and enrollment of elderly individuals. This estimate is conservative, not accounting for the rise in the number of non-elderly trial participants or the additional profits from faster participant enrollment and increased drug utilization.

The benefits of increased representation are most compelling if they shape product utilization and patient outcomes. In related work, Aslan et al. (2022) provide survey results indicating that greater levels of black patient enrollment increases doctors' stated 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 high Medicare share diseases, relative to both low Medicare share 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 differences.

Our paper contributes to the literature on representation in research and innovation (see, for example, Green et al. (2022) and Hutchins et al. (1999)). Firstly, our paper provides causal, large-scale evidence of how financial incentives shape representation in R&D. Our work is also related to Michelman and Msall (2022), who show that removing the US Food and Drug Administration's (FDA) guidance against inclusion of women of child-bearing potential in clinical trials increases the number of female-specific patents. However, they find no impact on female-focused clinical trials and do not observe enrollment criteria, suggesting that the financial incentives we study may be more salient than regulatory guidance. Recent work shows that shows that female-lead projects enroll more female participants (Gupta, 2022) and are associated with fewer adverse events (Hermosilla,

2023), but do not investigate the causal effects of a policy on participant representation.

Second, we provide empirical evidence that representation in the R&D process matters for product adoption. Recent work by Aslan et al. (2022) show through survey evidence that representation affects utilization for one under-represented group (Black Americans). We build on this by confirming their findings are applicable in another important setting using real-world prescription outcomes. Other related work has found that representation in inventors matters for project development and firm outcomes (Nielsen et al., 2017; Cao, Koning and Nanda, 2023). For example, Koning, Samila and Ferguson (2020, 2021) find that female inventors are more likely to innovate in areas that serve women's needs. We focus on the effects of funding—a key input to the innovation process—rather than innovators.

Finally, we shed new light on the role of public health insurance expansions in shaping innovation. Previous studies have primarily focused on how insurance can influence pharmaceutical innovation by shifting expected demand (e.g., Blume-Kohout and Sood (2013)). However, to our knowledge, ours is the first to examine how expanding insurance coverage affects the supply of inputs (i.e., user groups) in the R&D process and how this influences 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 uses subsets of diseases or cross-sectional evidence (Unger et al., 2006). 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 the number of trials, patient enrollment, and drug utilization suggest that reducing financial barriers to patient enrollment could be effective for increasing representation in clinical trials. Our findings suggest that policy interventions aimed at lowering financial frictions may be effective levers for shaping representation in the product development process.

2 Institutional Background

2.1 Drug Development

In the US, 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 drug 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 can 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 drug 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 $37,000 per patient (for Phase I) to $308,000 per patient (for Phase III) (Sertkaya et al., 2016). Drug manufacturers aim to enroll eligible participants quickly, due to competition also seeking to recruit the same patients and to minimize the high fixed costs associated extended trial recruitment periods.[3] For example, a Johns Hopkins report cites annual IRB fees up to $2,580, monitoring visit fees of $737 per day, annual administrative fees of $4,422 and many more. [4]

Before 2000, the costs of patient recruitment and retention were often shared between drug manufacturers and participants (Pear, 2000). While there is limited information on the actual allocation of costs and substantial variation, drug manufacturers typically cover routine clinical

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

[4]https://www.hopkinsmedicine.org/-/media/research/documents/offices-policies/crss-standard-costs-and-fees-fy2024-v2-04-august-2023.pdf

trial expenses and data analysis (Aaron and Gelbrand, 2000). Routine costs account for the bulk of the cost of most clinical trials and include room and board for hospitalized patients, diagnostic and laboratory tests, post-surgical care, and office visits (Aaron and Gelbrand, 2000). Participants, on the other hand, usually receive treatments with minimal cost, but they may still bear the costs linked to some routine care, screening, and travel. Insurers and Medicare occasionally covered clinical trial costs. However, insurers would often argue that clinical trial treatments are experimental and would not cover the routine clinical trial expenses for participants. Before 2000, Medicare did not cover the routine costs of clinical trials. In 2000, about 17% of Medicare patients had a Medicare Advantage plan, and private insurers also historically did not cover these costs.

The uncertainty surrounding the financial responsibility associated with clinical trials is often cited as a factor that discourages potential participants or results in significant unexpected costs for those that join trials (Pear, 2000). For example, clinical trial investigators cannot assure elderly prospective participants that Medicare will cover the costs associated with trial participation, a risk that must be communicated during the informed consent process (Aaron and Gelbrand, 2000). Additionally, Medicare's policy of not routinely preauthorizing care and its legal status as a payer of last resort means trial participants may incur significant costs if Medicare denies their claims. Taken together, this creates substantial uncertainty for both participants and drug manufacturers. Drug manufacturers also faced high costs: to address some of this uncertainty, about one-third of all industry trials were fully funded and covered all routine costs without billing insurance.[5]

2.3 Representation of the Elderly In Clinical Trials

The high costs and uncertainty of insurance coverage may have contributed to the limited participation of elderly participants in clinical trials. Although individuals aged over 65 constitute 16.8 percent of the U.S. population, they account for just 5 percent of participants in the median trial in our dataset (U.S. Census Bureau, 2023). Individuals aged over 65 have been reported to be underrepresented in a various diseases, including cancer, diabetes, heart failure, and osteoporosis (Hutchins et al., 1999; Lau et al., 2022). This underrepresentation raises concerns about potential

[5]Source: Author's interviews with UCLA clinical trial managers.

underinvestment in safe and effective treatments (Shenoy and Harugeri, 2015). Additionally, underrepresentation of elderly trial participants has the potential to shape utilization, due to dissemination of clinical trial information through drug labels, public registries, publications, and advertisements.

Beyond the cost-related reasons described above, the elderly encounter obstacles related to logistics, comorbidities, health literacy, and cognitive limitations in decision-making (Herrera et al., 2010). Challenges include hearing impairments affecting communication with researchers, physical immobility impacting transportation to trial sites, and the urban-centric location of clinical trials, which may pose difficulties for elderly individuals who are more likely to reside in rural areas. Most trials exclude participants with some comorbidities, and the elderly are more likely to have disqualifying health conditions.[6] A homogeneous trial population decreases the variance of treatment effects and therefore the sample size needed for statistical power. As a result, including the elderly may add additional costly variability.

2.4 Medicare Memorandum of 2000

In June of 2000, President Clinton ordered Medicare to start covering most of the costs of clinical trials for its beneficiaries (largely patients aged 65 and older). 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." This memorandum includes items or services typically provided absent a clinical trial, such as conventional care during a trial. This also includes monitoring of the effects of the investigational drug or service, items required for the provision of the investigational drug or service, and costs related to the diagnosis and treatment of complications. Drug manufacturers would continue to pay for the collection and analysis of data and the investigational item or service itself.[7]

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). This memorandum also included an informational campaign to inform Medicare beneficiaries, doctors, hospi-

[6]The elderly are also less likely to be willing to accept treatments with side-effects such as nausea or fatigue (Lara et al., 2001).

[7]See National Coverage Determination (NCD) for Routine Costs in Clinical Trials (310.1)

tals, and other health care providers of the new policy. The intended impact of this policy was to decrease uncertainty and increase subsidization of clinical trial costs for both elderly patients and drug manufacturers. Specifically, patients were assured that their routine costs were covered and manufacturers could bill Medicare instead of risking covering costs themselves.

3 Data

We are interested in measuring how the Medicare Memorandum of 2000 shifted innovation and enrollment for a given disease. We define diseases using the International Classification of Diseases, version 9 (ICD-9).[8] Our final dataset consists of 424 ICD-9 codes.

1. **High Medicare Share Diseases:** Following a commonly used approach (e.g., Acemoglu et al. (2006), Duggan and Morton (2010), Blume-Kohout and Sood (2013), and Krieger, Li and Papanikolaou (2022)), we proxy for exposure to the memorandum by calculating the share of individuals covered by Medicare associated with each ICD-9. We use the 1996 (the earliest year in which data is available) to 1999 MEPS, a nationally representative survey of the U.S. civilian non-institutionalized population. We categorize diseases as having a "high Medicare share" if they have more than the median share of Medicare individuals with that diagnosis.[9] Appendix figure A.1 presents the distribution of Medicare shares across diseases. For example, low Medicare share diseases ("young diseases") include attention-deficit/hyperactivity disorder (ADHD) has a 3 percent Medicare share and the common cold has a 8 percent Medicare share. In contrast, high Medicare share diseases ("old diseases") include vitamin D deficiency (54 percent Medicare share) and Parkinson's disease (81 percent Medicare share).

2. **Clinical Trials and Participant Enrollment:** To create a dataset of clinical trials and participant enrollment, we begin with the data from the Cortellis Clinical Trials Intelligence

[8]Examples of diseases at the ICD-9 code level include "malignant neoplasm of the colon" and "diabetes mellitus."

[9]For simplicity, we focus on categorizing diseases into two categories: high vs. low Medicare share. Our results are robust to using a continuous measure as in appendix figure A.2

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 codes. We incorporate ClinicalTrials.gov data on clinical trial enrollment characteristics, such as the number of elderly (aged 65 and over) and non-elderly participants (see appendix figure A.3 for an example). We restrict the sample to trials from 1995-2010 since data are sparse in earlier years. We also limit to trials with at least one location in the United States, since the Medicare memorandum was a US-based policy.[10] This results in a final dataset of 10,058 trial-diseases with clinical trial enrollment information.

3. **Drug Utilization:** To analyze how drug utilization shifts among high Medicare share diseases, we collect data on drug utilization from the 1996 to 2010 MEPS surveys. We first categorize drug utilization from three categories of individuals: those aged 65+, 64 and below, and 55 and below. We next classify prescription drugs in the MEPS as primarily related to old or young diseases. We link MEPS drug names to clinical trials in the Cortellis data, which provides information on the diseases tested and the drug's approval status by indication. We assign a drug to the disease for which it was initially approved by the FDA. As above, we identify high and low Medicare share diseases based on the share of Medicare patients with that disease diagnosis. Consequently, a prescription drug in MEPS can be categorized as treating a disease with either a high or low Medicare share.

4. **Disease Burden:** To determine under and over-representation of elderly individuals across diseases, we compute each ICD-9's average disease burden by incorporating data from The Global Burden of Disease (GBD) dataset. While the GBD dataset is one of the most comprehensive datasets on disease incidence available, there are some limitations: disease burden is measured with noise, aggregated from a variety of sources and frequently unavailable, which is why we use a cross-section from 2019 instead of historical data.[11] While we focus on disease burden among the elderly, we also compute disease burden by race and gender for

[10] We drop trials that occur in other countries, since we do not take a stand on whether international pharmaceutical investment is a complement or substitute for US-based investment.

[11] Disease burden is an imperfect proxy of a disease's potential market size, since market size is disease

complementary analyses.

Using this data, we construct a panel dataset at the disease-year level. Appendix table A.1 shows that the average disease-year has 5.2 total clinical trials, which enroll an average of 62 non-elderly individuals and 26 elderly individuals. To investigate drug utilization, we also construct a dataset at the patient-year level. On average patients have 0.8 unique prescriptions for young diseases and 2 unique prescriptions for old diseases.

4 Documenting Disparities in Clinical Research

We begin by examining age disparities in clinical trial enrollment relative to disease burden prior to the 2000 memorandum. This analysis uses data from 1995 to 1999. For each ICD-9 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 ICD-9-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. 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 high Medicare share diseases and the inclusion of elderly participants in those trials. We then explore how changes in trial participant representation shaped drug utilization.

burden interacted with access to health care and willingness to pay for treatment.

5 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 DID specification compares outcomes in ICD-9 codes with an above median share of Medicare recipients versus a below median share of Medicare recipients, before and after the Medicare Memorandum of 2000:

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

where j is ICD-9 disease code and t refers to calendar years. The outcome y_{jt} presents log trial counts or log trial enrollment counts within a disease and year, as trial counts and enrollment have a skewed distribution. The coefficient $HighMcareShare_j$ is an indicator for whether the ICD-9 code had an above median share of Medicare patients before 2000. 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 $HighMcareShare_j$. The regression also includes controls for whether the ICD-9 code had an above median share of Medicare patients, ICD-9 fixed effects (δ_j), and year fixed effects (δ_t). To account for time-varying differences across disease markets (e.g., shifts in the size of patient groups, research costs, scientific opportunities), we include interactions of linear year with the ICD-9 disease chapter, which is a broader ICD-9 categorization ($\delta_{c(j)}$).[12] Standard errors are clustered at the ICD-9 level.

For the set of coefficients, β_t, to represent the causal impact of the memorandum on clinical trials, ICD-9 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

[12]For example, the ICD-9 disease chapter for the ICD-9 code "malignant neoplasm of the colon" is "neoplasm."

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 at the end of section 5.2.

Before proceeding to our event-study 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 noticeably 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. In particular, we estimate Equation (1), where the outcome is the log(1+total number of clinical trials) in a disease and year. Figure 2 shows that 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. Corresponding estimates in table 1 reveal that the memorandum is associated with an 18 percent relative increase in the number of clinical trials in diseases with high Medicare share in each year after the memorandum.

The effect of the memorandum on the log number of trials in old diseases stops increasing after 2005. This is partially because the total number of clinical trials initiated each year grows, so a given increase in clinical trials becomes a smaller percent of the total trials. In addition, in 2005 Rush University Medical Center, Weill Cornell Medical Center, and the University of Alabama at Birmingham settled federal lawsuits regarding inaccurate Medicare billing for clinical trials. Consequently, trial sponsors were increasingly cautious about Medicare billing. Many undertook extensive and costly Medicare Coverage Analysis determinations for each trial, which reduced the

financial benefit of the policy [13]

We evaluate the robustness of our results in relation to other shocks. Consistent with the view that our results are not driven by the introduction of Medicare Part D, figure 2 shows that the increase in trials in diseases with above median elderly diagnoses occurs several years before 2003 (the year the Medicare Modernization Act was signed into law). We also conduct two additional robustness tests: 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 the introduction of Medicare Part D in 2006. 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 using an alternative, continuous measure of exposure to the memorandum (see appendix figure A.2), to examining the total number of trials (see appendix figure A.6), and to looking at individual trial phases (see appendix figure A.7).

Finally, we investigate the concern that projections about the United States elderly population shifted around 2000. If demand for pharmaceuticals by elderly patients were projected to increase, this might motivate more innovation in elderly diseases. However, the 2000 census did not show large gains in elderly population. From 1990 to 2000, the growth of the elderly population was 12.0 percent, compared to the total population growth of 13.2 percent.[14] In 2000, the baby boomers, defined as those born 1946-1964, would still be aged 36-54 and projections about their age patterns did not change discretely.

5.3 Impact on Clinical Trial Representation

In this section, we document evidence that the memorandum shifted drug manufacturers' trial recruitment priorities and increased the quantity of the elderly participants enrolled within each trial.

Panel A of figure 3 examines the impact of the memorandum on drug manufacturers' patient recruitment priorities, by examining changes in trial enrollment criteria. Each clinical trial has spe-

[13] Source: Author's interviews with clinical trial managers at UCLA.

[14] https://www.census.gov/newsroom/releases/archives/2010_census/cb11-cn192.html

cific enrollment criteria listing eligible participants (e.g. "Female", "Ages 18-44", "Type 2 diabetes", and "ability to walk 30 m independently"). We categorize trials as prioritizing elderly participants if the enrollment criteria include *any* adults at age 65 or over, encompassing trials with only elderly participants or both elderly and non-elderly participants. We compare the impact of the memorandum on these trials against those whose enrollment criteria include *only* non-elderly participants. Panel A of figure 3 demonstrates that increased exposure to the memorandum is associated with an immediate and sustained increase in the number of trials enrolling any elderly participants.

Columns 2 and 3 of table 1 present seemingly unrelated regressions, which permit a direct comparison on coefficients. Among affected diseases, there was a 27 percent yearly increase in the number of trials recruiting any elderly participants and little impact on trials recruiting non-elderly participants. 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 age categories. 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. 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 translated to an increase in the *actual* quantity of elderly participants enrolled in each trial, we analyze how patient enrollment within a trial evolved following the policy. Panel B of figure 3 and Columns (3) and (4) table 1 show the policy's effect on the enrollment of elderly vs. non-elderly participants per trial. The number of elderly participants enrolled increases by nearly 60 percent. Highlighting potential positive spillovers across trials participant groups, the increase in the number of non-elderly participants also increases and is not statistically significantly different from the increase in elderly participants. These trends also correspond to a shift in age disparities in clinical research that occurred after the memorandum: appendix figure A.9 reveals a general decline in age disparities in clinical trial enrollment relative to the disease burden after 2000, compared to earlier years.

The benefit of figure 3 is these figures include the full sample of trials for which we have enrollment criteria (panel A) or patient enrollment information (panel B). A drawback is that some

age groups may be partially treated if there are spillovers from elderly trial enrollment onto near-elderly trial enrollment. Appendix figure A.10 presents enrollment patterns for the subset of trials that enroll (only) those aged over 65 or (only) those aged under 55. In contrast to the increase we document in over-65 year old patient enrollment, there is no statistically significant increase in under-55 patient enrollment.[15]

Taken together, these findings suggest that the memorandum lowered the expected costs of enrolling elderly participants. As a results, firms responded by conducting larger clinical trials for high Medicare share diseases. 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 increased the enrollment of both elderly and non-elderly participants.

Our analysis focuses on the total enrollment of elderly individuals in trials, rather than disparities between the enrollment in trials and the global diseases burden. This is partially because the global disease burden may be an imperfect proxy of the potential market size for a disease and is frequently unavailable. Another reason is that elderly individuals were under-represented in almost all diseases before 2000 (see figure 1), so increasing elderly participation in almost any disease is moving towards more equitable representation.

6 Impact on Drug Utilization

A recent literature has suggested that increases in representation in the R&D process may influence product adoption and utilization (Alsan and Wanamaker, 2017). The results of clinical trials are often used in marketing materials by pharmaceutical firms. In marketing material, 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 physician's own research and may recommend products with recent representative evidence to elderly patients. For this analysis, we compare drug utilization among elderly versus middle-aged individuals, before and after the implementation of the Medicare Memorandum of 2000. We regress

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

[15]The enrollment criteria categories are too broad to permit smaller age bins than in figure 3 panel A.

where y_{it} is the natural log number of unique prescriptions (plus one) among either old or young diseases. This regression is at the individual-year level. Prescriptions are matched to ICD-9 codes and then old or young diseases as described in section 3. 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, and η_i refer to person-level controls for race and ethnicity. Standard errors are robust.

Figure 4 shows that following the 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 the survey evidence from Alsan and Wanamaker (2017), but replicate these conclusions using real-world outcomes.

By 2005, the year before Medicare Part D was implemented, figure 4 shows that elderly individuals took about 16 percent more prescriptions in high Medicare share diseases than before the Medicare memorandum. In 2003, the year Medicare Part D was announced, this figure was already about 13%. Figure A.11 presents estimates using levels of prescriptions. In 1999, the average elderly individual took 2.2 unique prescriptions in a high Medicare share diseases. The increase of 0.5 unique prescriptions for elderly individuals represents a 23 percent increase and is similar to the estimates from figure 4.

Other literature has found that the implementation of Medicare Part D in 2006 also resulted in an increase in drug utilization, though these estimates are often statistically insignificant (Duggan and Morton, 2010) and confounded by stockpiling for chronic prescriptions (Alpert, 2016). We use different methodological choices but also find a small uptick in prescriptions after 2006 in figure 4, though these estimates are not statistically significantly different than those before the implementation of Medicare Part D.

7 Discussion and Conclusion

Amid rising public pressure, policy makers and researchers are exploring strategies to minimize demographic disparities in the innovation process. Our study investigates how insurance policies influence representation in drug development. Diseases more affected by the memorandum see a 20

percent increase in the number of clinical trials. Within these diseases, firms expanded their clinical trial enrollment criteria to include elderly patients. This resulted in a significant increase in both elderly patients and non-elderly patients. We also observe a significant increase in drug utilization among the elderly, suggesting that the Medicare-driven shift in representation could meaningfully shift drug utilization patterns.

Our results have several important insights that future research could extend. First, to quantify the true welfare costs of the memorandum, future work should distinguish whether this comes from an overall increase in innovative activity and drug utilization in affected diseases, or a reallocation from less to more affected diseases. Second, future work should examine how the Medicare Memorandum of 2000 shapes representation at drug-level. Third, a direct analysis into how increases in representation might shape the underlying quality and precision of evidence generated and the direct impact on patients outcomes is an important topic for future research.

More broadly, our results on age-concordance offer valuable insights into how policies might improve concordance on other demographic dimensions in product development. For instance, low-income individuals are underrepresented in clinical trials. In January 2022, Medicaid began to cover routine costs for its recipients participating in clinical trials, potentially shifting the representation of low income individuals (Takvorian, Guerra and Schpero, 2021). Our results suggests carefully designed policies may effectively address significant and long-standing underrepresentation in the innovation process.

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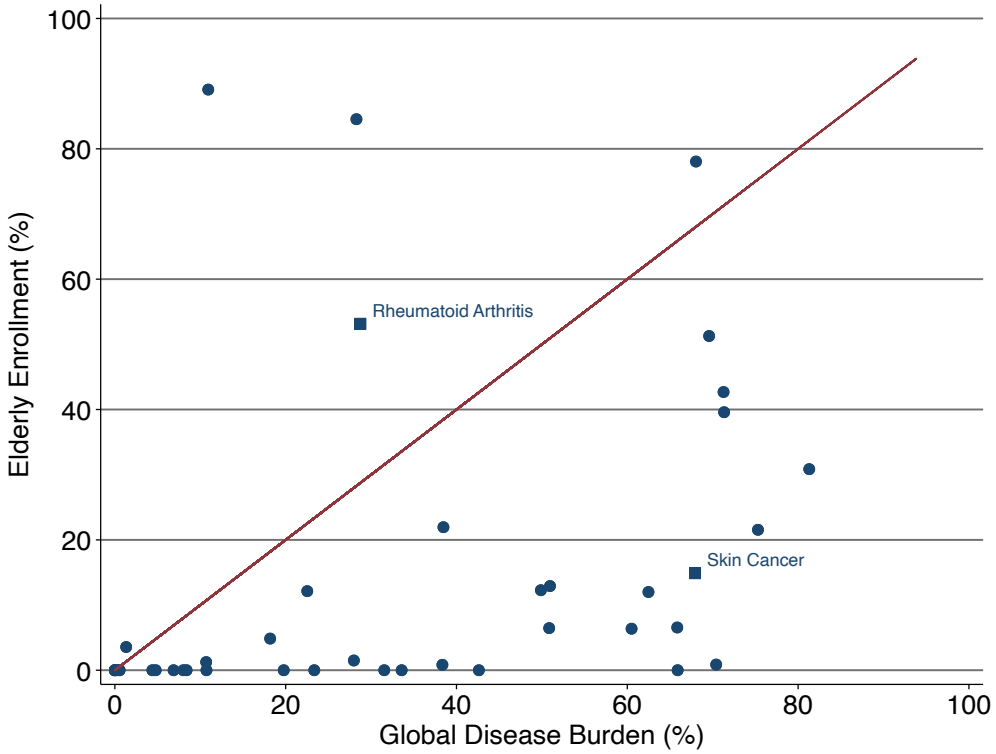
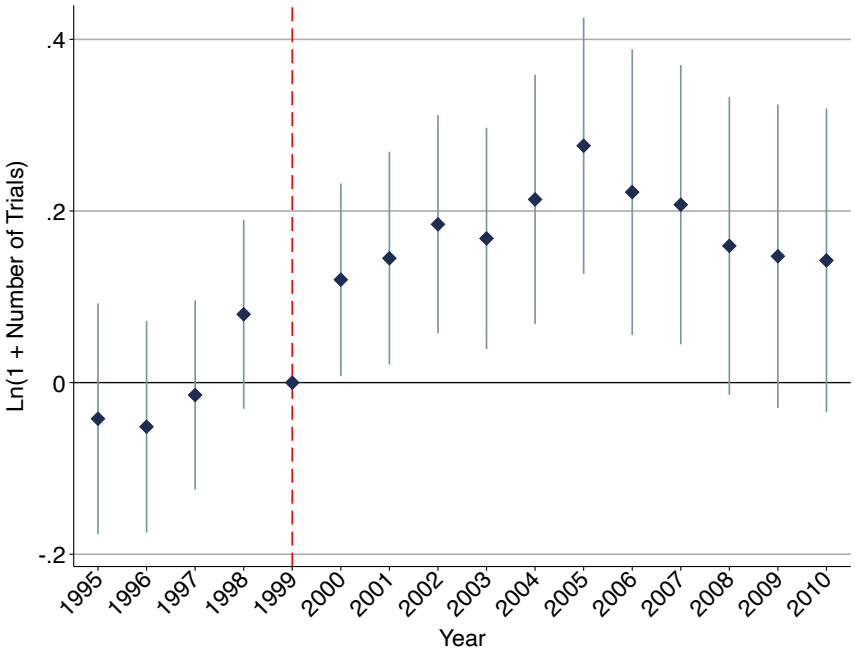
Figures and Tables

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



Note: Each point represents an ICD-9 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.

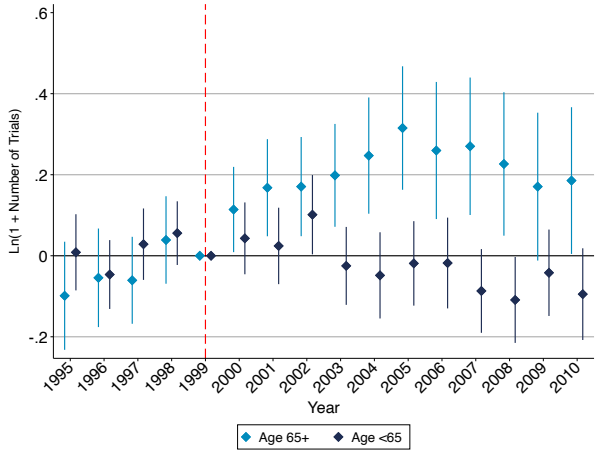
Figure 2: Impact of Medicare Reimbursement Expansion on Ln Total Number of Trials: Event Study



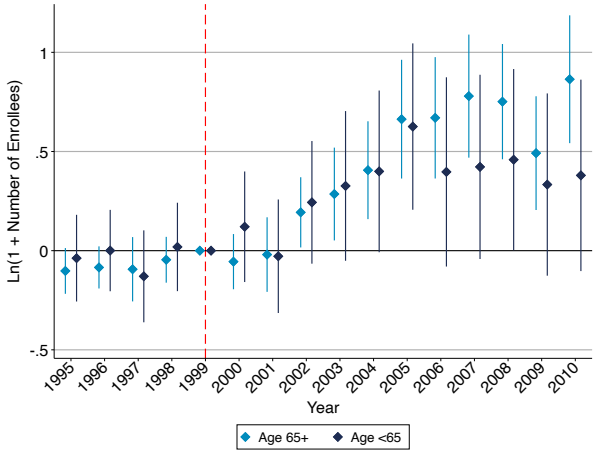
Note: Figure presents event study coefficients from the estimation of equation 1. We plot the coefficients on the interaction between year and an indicator for whether a disease had above median share of diagnoses among the elderly from 1996-1999. An observation is a disease-year and the outcome is the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

Figure 3: Impact of Medicare Reimbursement Expansion: Mechanisms

(a) Trials, by Enrollment Criteria

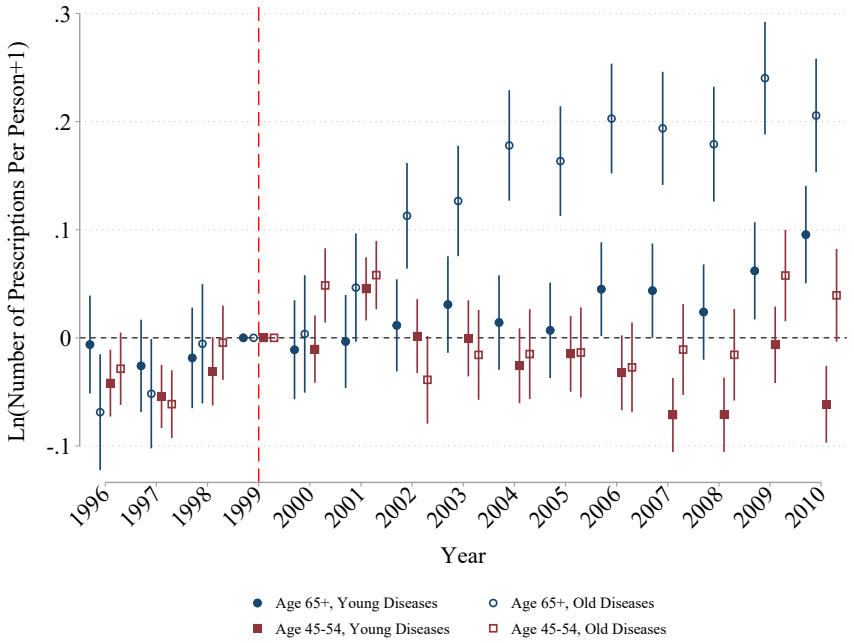


(b) Number of Participants Enrolled



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: Log 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 the natural log of the number of unique prescriptions per person (plus one) in diseases with an above median share of diagnoses among the elderly ("Old diseases"), or in diseases with a below median share of diagnoses among the elderly ("Young Diseases").

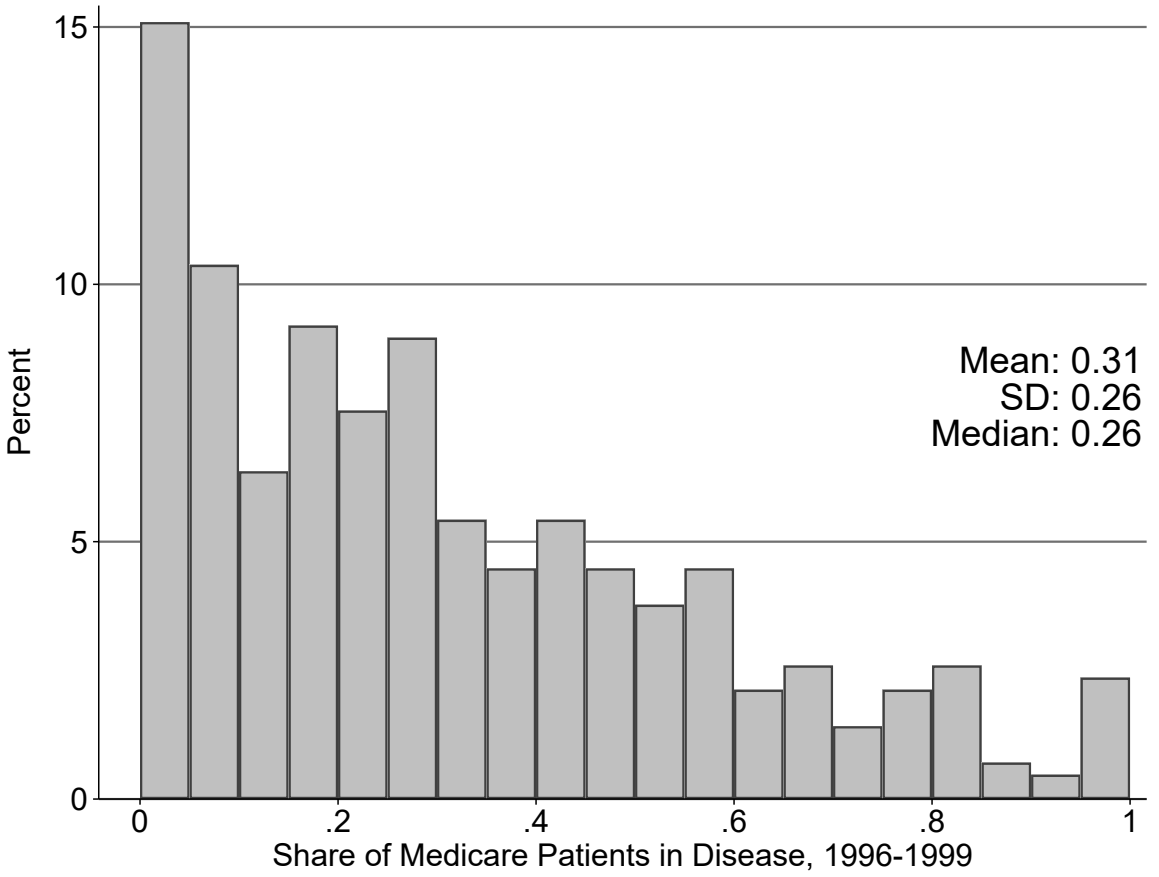
Table 1: Impact of Medicare Reimbursement Expansion

	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.

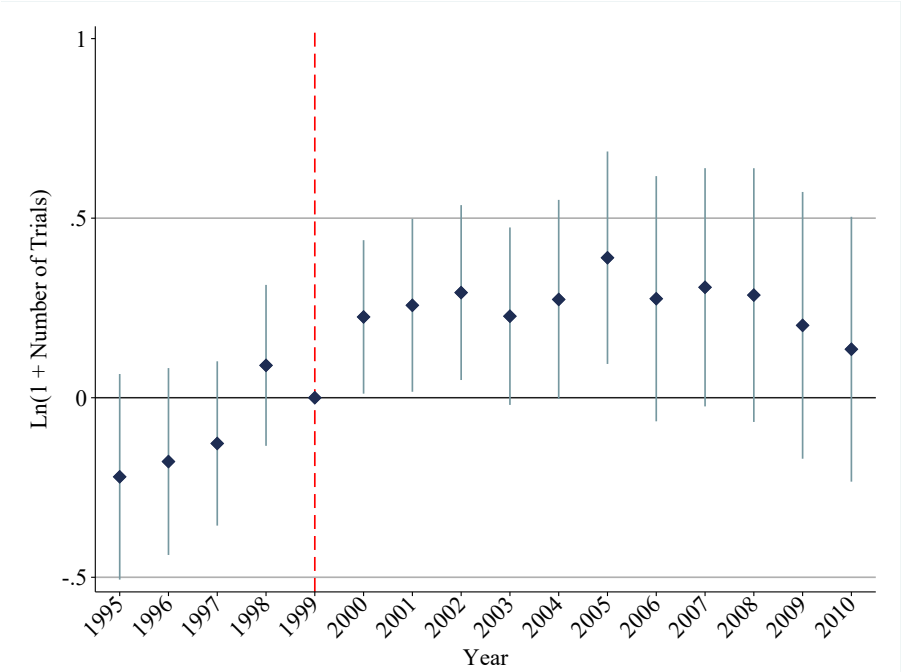
A Appendix

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



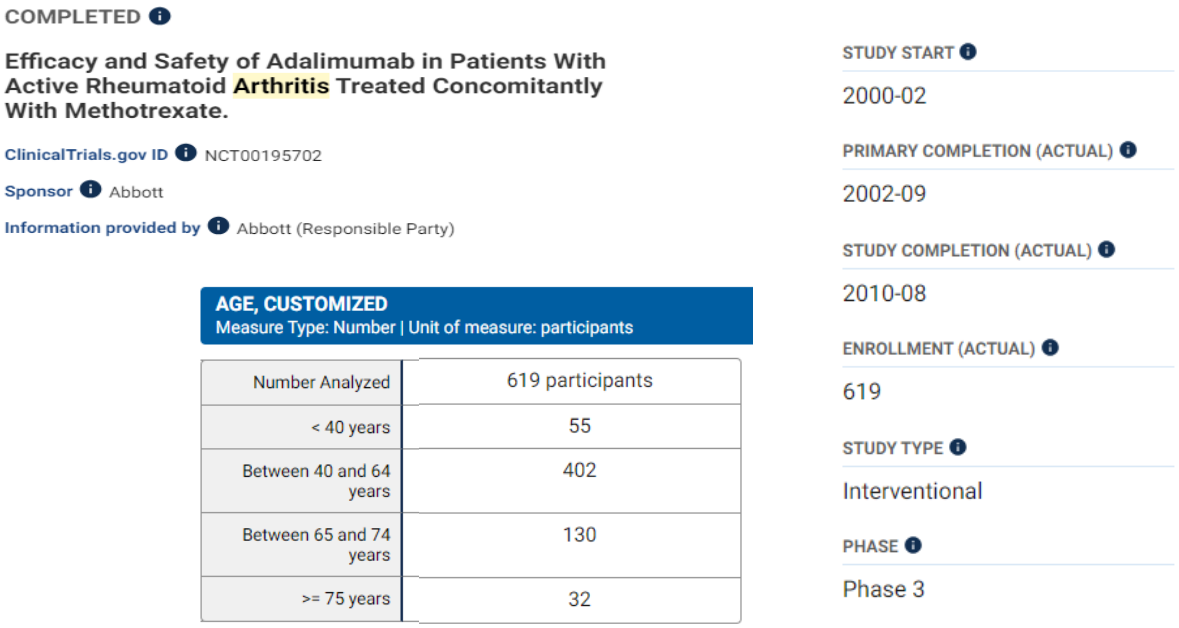
Note: Figure plots the share of diagnoses in a disease among Medicare patients. The sample used is the MEPS from 1996-1999.

Figure A.2: Impact of Medicare Memorandum using Continuous Medicare Share



Note: Figure is similar to figure 2, but 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-year and the outcome is the natural log of the number of trials in a disease year.

Figure A.3: 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

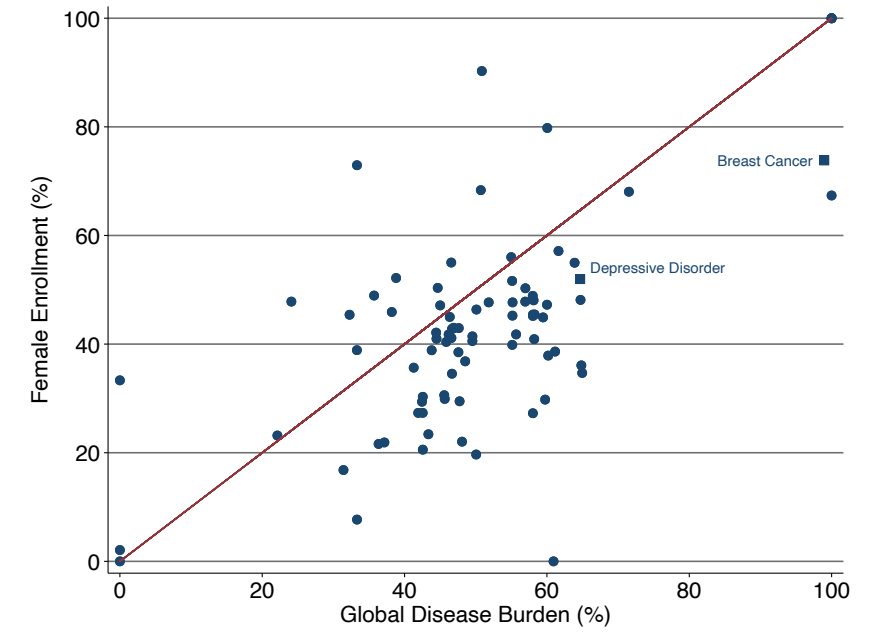
STUDY TYPE
Interventional

PHASE
Phase 3

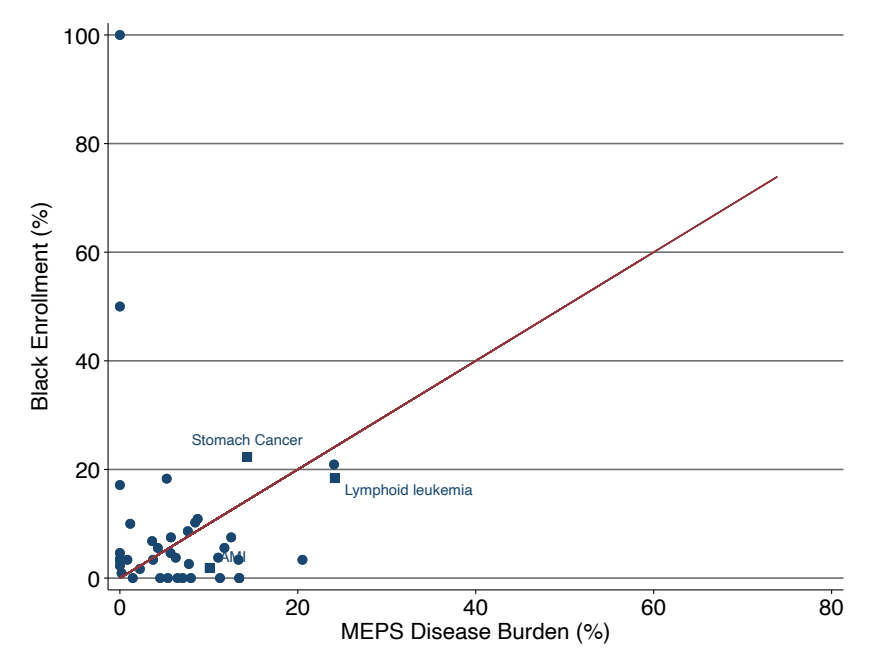
Note: Figure shows an example of trial enrollment counts in ClinicalTrials.gov. This trial was a phase 3 trial testing the efficacy of adalimumab. The trial was conducted in 2000, and adalimumab (brand name Humira) was approved by the FDA in 2002. This trial enrolled 130 individuals aged 65-74 years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

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

(a) Gender

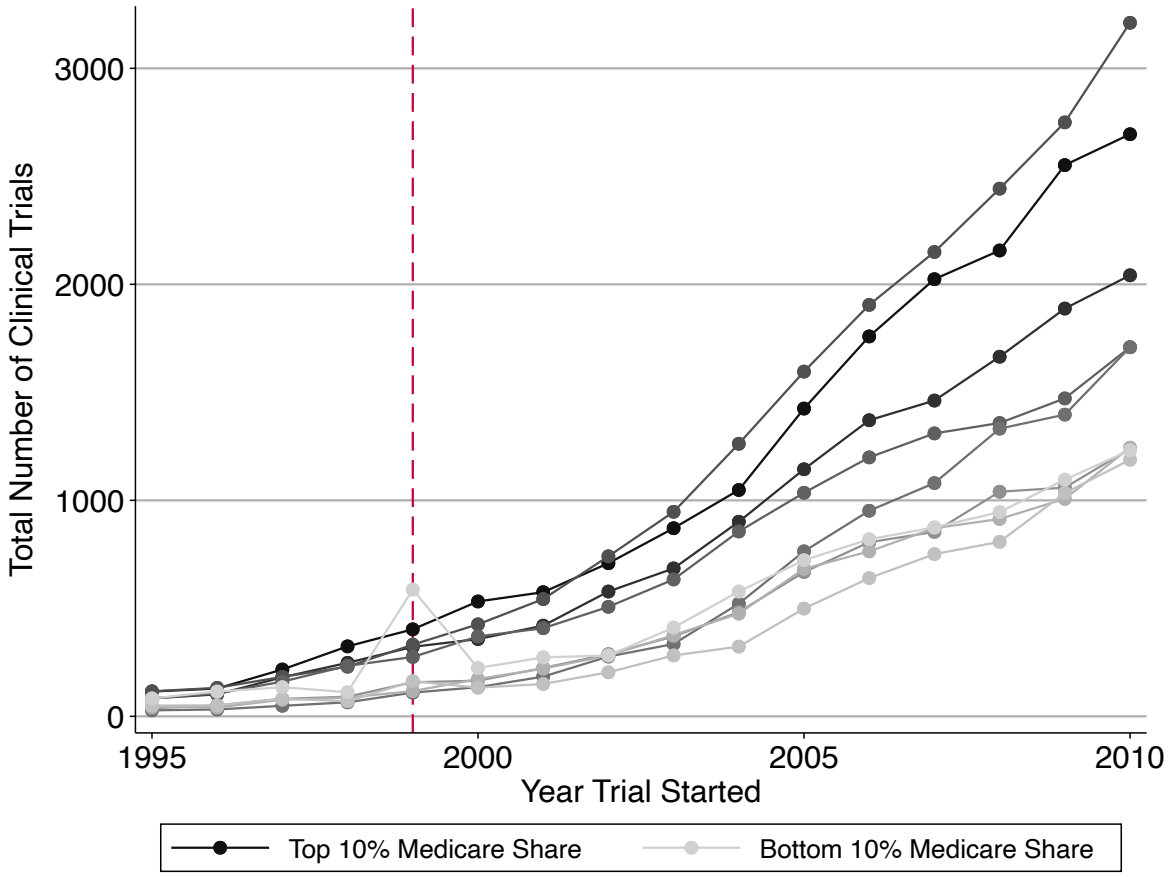


(b) Race



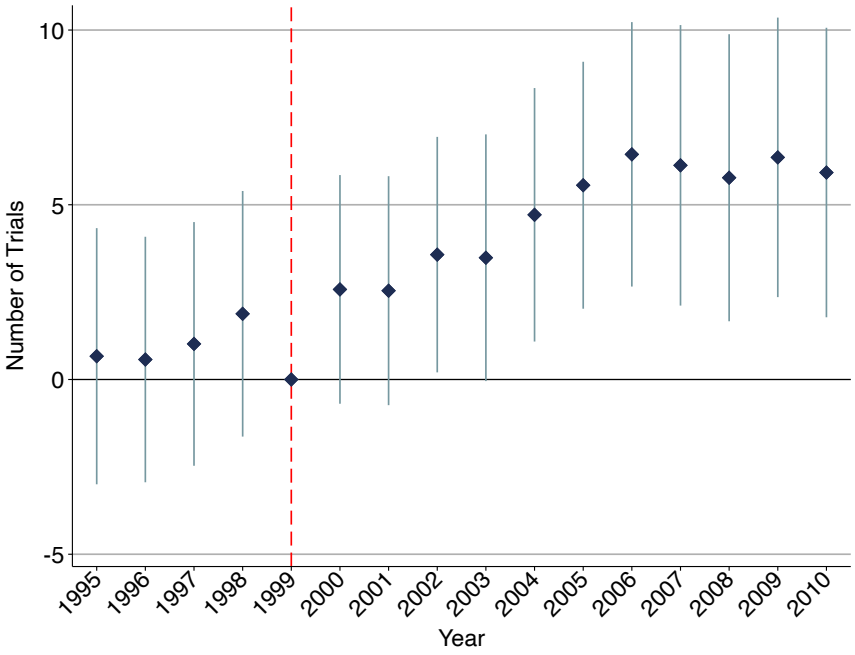
Note: Each point represents an ICD-9 code, with the x-axis showing the share of disease burden among women (panel a) or black individuals (panel b). The y-axis presents the average enrollment among women (panel a) or black individuals (panel b) in clinical trials for those diseases, between 1995-1999. 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



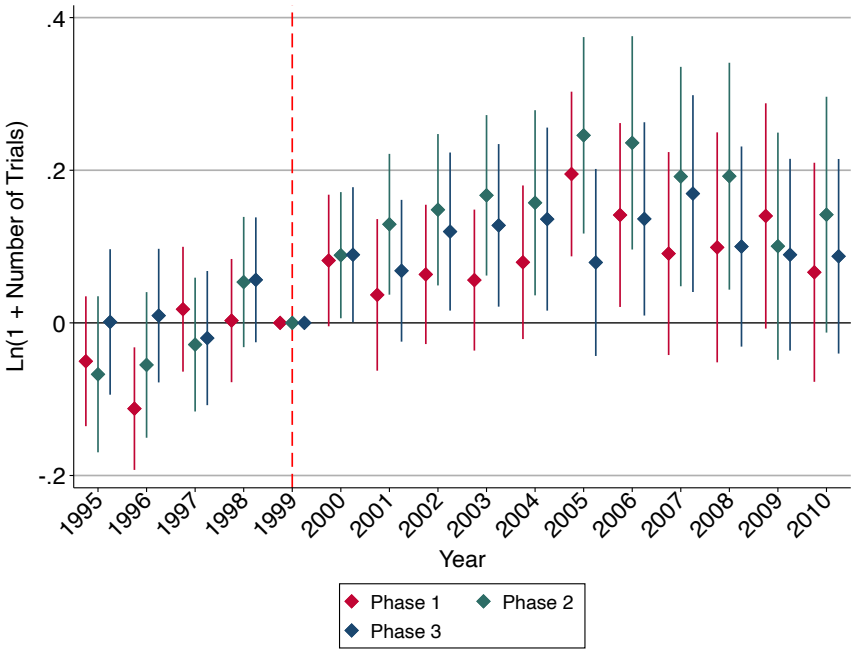
Note: Figure plots the total number of clinical trials within disease categories. The darkest line refers to diseases in the top 10 percent of Medicare share of diagnoses. The second-darkest contains the diseases in the top 10-20 percent of Medicare share of diagnoses all the way down to the lightest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



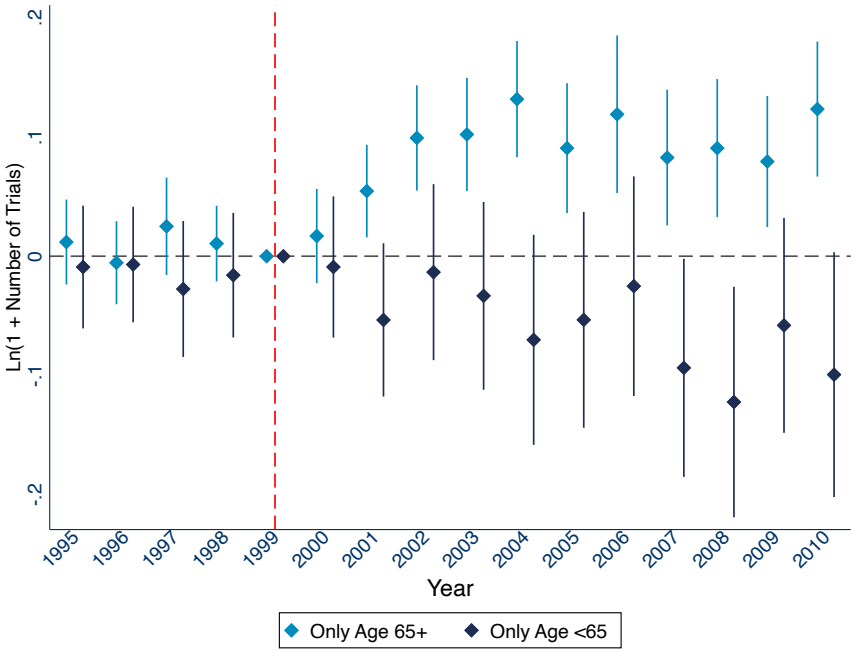
Note: Figure presents event study coefficients from the estimation of equation 1. We plot the coefficients on the interaction between year and an indicator for whether a disease had above median share of diagnoses among the elderly from 1996-1999. An observation is a disease and year and the outcome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



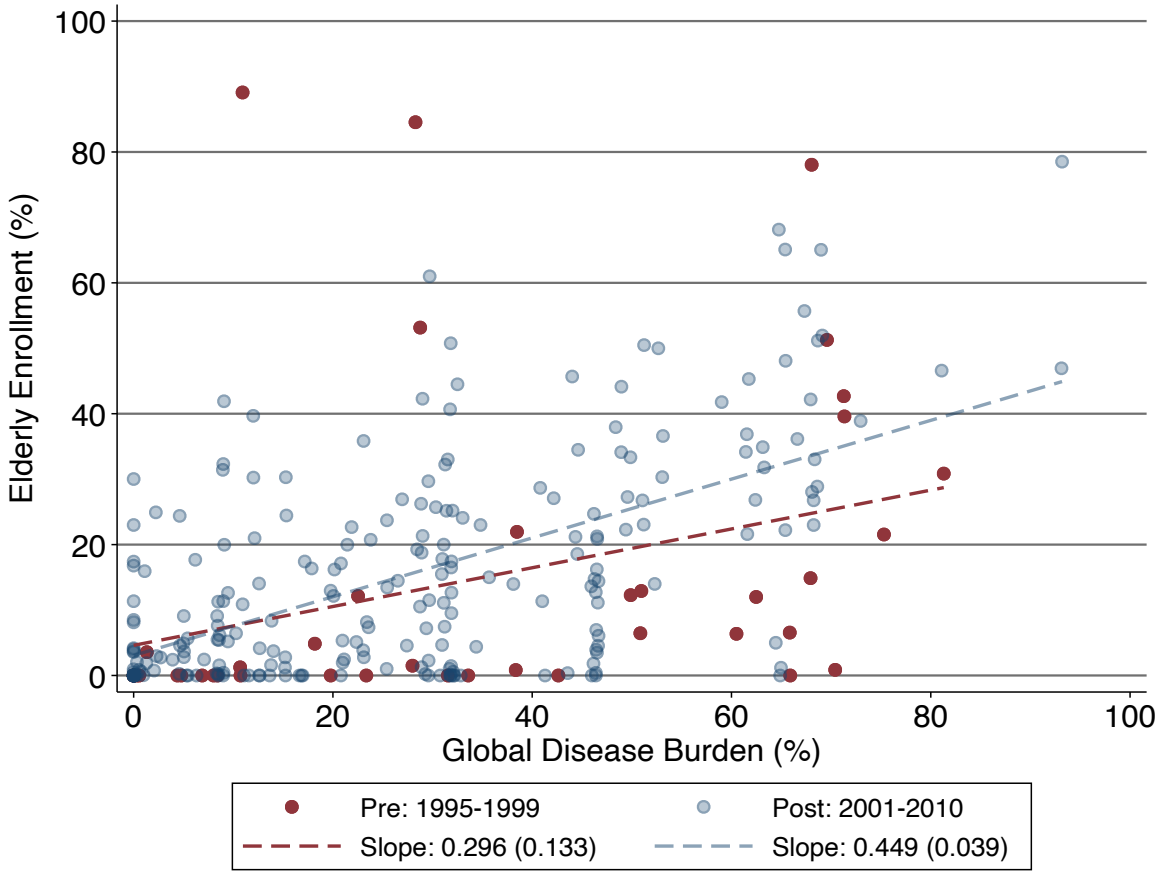
Note: Figure presents event study coefficients from the estimation of equation 1. We plot the coefficients on the interaction between year and an indicator for whether a disease had above median share of diagnoses among the elderly from 1996-1999. An observation is a disease and year. The outcomes are 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: Enrollment Criteria, Only 65+ versus Only Under 65



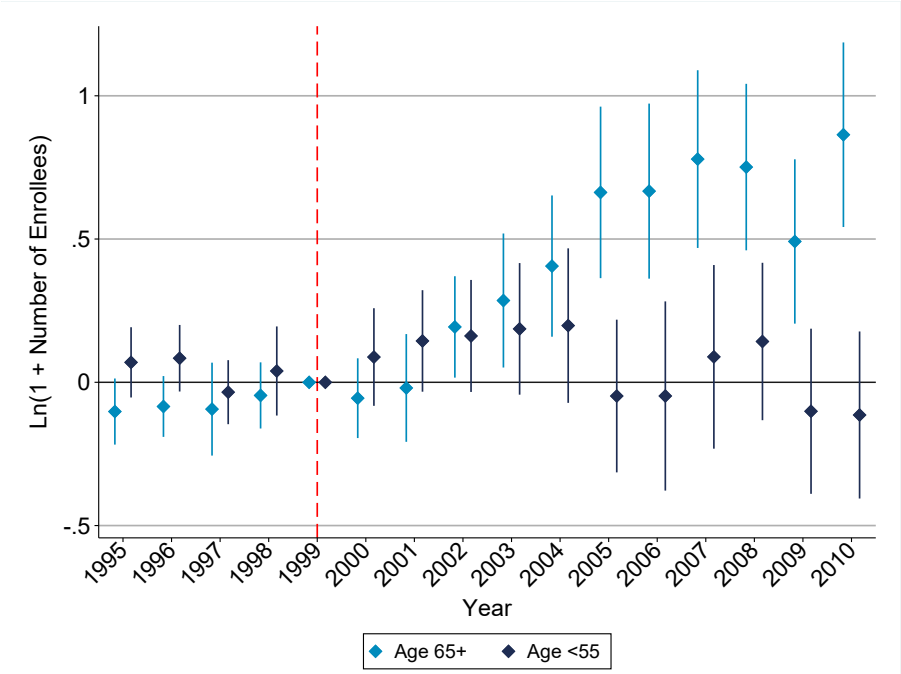
Note: Figure presents event study coefficients from the estimation of equation 1. We plot the coefficients on the interaction between year and an indicator for whether a disease had above median share of diagnoses among the elderly from 1996-1999. An observation is a disease and year. This figure presents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



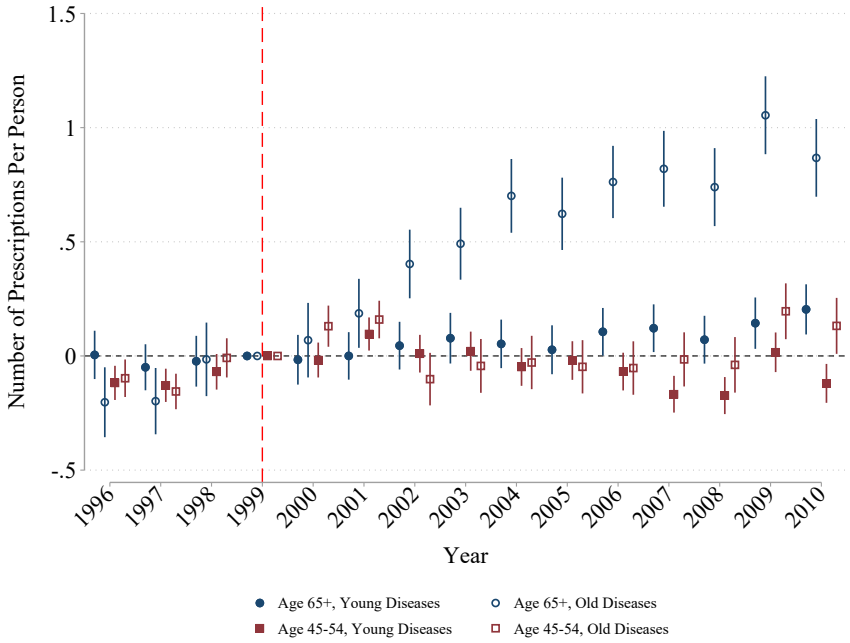
Note: Each point represents an ICD-9 code, with the x-axis showing the share of disease burden among the elderly (aged 65+) and the y-axis presenting the average share of elderly participants in clinical trials for those diseases. The maroon dots average across 1995-1999 while the navy dots average across 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.

Figure A.10: Patient Enrollment, Over 65 vs Under 55



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 participants who are elderly ("Age 65"); in another the outcome is the natural log of participants who are exclusively under 55 ("Age <55"). This figure includes a subset of the data from figure 3.

Figure A.11: 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 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) is estimated using OLS. Columns (2)-(5) estimated using seemingly unrelated regressions.