Localized Knowledge Spillover and New Drug Adoption: Evidence from Clinical Trial Sites*

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Abstract

Clinical trials benefit patients directly by providing novel treatments, but little is known about the indirect effects of clinical trials on physician prescribing through localized knowledge spillover. This study examines whether exposure to a clinical trial of a new drug in a physician's local geographic area affects the physician's propensity to prescribe the drug, i.e. a localized knowledge spillover from clinical trial sites to physician. Utilizing the Medicare Part D prescribing patterns of more than 10,000 physicians across 29 new cancer drugs approved by the US Food and Drug Administration between 2014 and 2019, we find that an exposure to clinical trials of new cancer drugs increases the likelihood that physicians prescribe these drugs by 0.18 percentage points, representing a 14% increase relative to the average prescribing rate. Notably, the localized knowledge spillovers are more pronounced when the proximate clinical trial site hosts the leading researcher of the clinical trial and the physician is affiliated with the proximate clinical trial site. There is no clear difference on the localized knowledge spillover between trials before and after FDA approval. Nonetheless, the localized knowledge spillover is stronger for physicians graduating from higher-ranked medical schools, and with more experienced physicians, and male physicians.

Keyworks: Clinical Trials Exposure; Prescribing; New Drug Adoption

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1. Introduction

The development of new drugs for disease treatment has been critical to the advancement of healthcare over the past 40 years (Kouvelis et al., 2017). Access to clinical trials provides an option for new drugs before they are approved for routine use. However, only 7% of adult cancer patients in the U.S. report participating in clinical trials (Unger et al., 2024) and clinical trial sites are distributed unevenly across the U.S. (Gu et al., 2024). Given its importance, policymakers are actively engaged in policies to expand geographical access to clinical trials.[1] A benefit-cost analysis of such policy requires the input of direct and indirect benefits of clinical trials. Direct benefits of clinical trials to patients, such as access to novel treatment (Roberts et al., 2004), are better understood, but indirect benefits of clinical trials to patients are less explored, which hinders the evaluation of related policy initiatives.

This study addresses this gap by highlighting an indirect benefit of clinical trials, i.e. facilitating diffusion of new drugs to physicians. Specifically, we examine how exposure to clinical trials of new drugs affects physicians' prescribing of those drugs after they are approved by the Food and Drug Administration (FDA). There is no clear theoretical prediction on how physicians would respond to the clinical trials of new drug conducted near them, which call for empirical investigation. On one hand, there is a long lag (of several years) from the beginning of clinical trials to publication.[2] During the research process, clinical trials produce scientific information, which only has localized spillover exhibiting a pattern like other new knowledge (Jaffe et al., 1993).

1 See the Decentralized Clinical Trials draft guidance from the FDA: https://www.fda.gov/regulatory-information/search-fda-guidance-documents/decentralized-clinical-trials-drugs-biological-products-and-devices

2 For instance, among the cancer drug studied in (McKibbin, 2023), the average length of a clinical trial is 2.8 years. The time between the completion of the trial and the first presentation of the results at a major conference, such as American Society of Clinical Oncology (ASCO) annual conference, is 1.55 years. It takes about 1.8 years and 2 years between the presentation at ASCO and publication and the presentation at ASCO and potential approval, respectively.

Physicians practicing close to the trial sites respond more than the other physicians because they experience localized knowledge spillover from the trial site. On the other hand, once the clinical trial results are published and the drug is approved by the FDA, the drug efficacy is expected to be known among physicians given the advances in information (Meinhofer, 2018) and communication technology and physicians are highly trained to access medical information (Oshikoya et al., 2011). There is no clear reason to believe distance to trial sites plays a role in physicians prescribing of new drug.

The empirical analysis is based on physician-Hospital Referral Region (HRR)-drug-year level data from Medicare Part D Prescribers – by Provider and Drug (*Medicare Part D Prescribers - by Provider and Drug | CMS Data*) for the period 2014–2019. Our dataset contains information, such as practice location and prescribing records, for over 10,000 oncologists and other physicians prescribing 29 new cancer drugs over sample period. To measure the clinical trials of new cancer drugs, we collect the trial sites and timing of each clinical trials conducted for those 29 drugs. The sample of Medicare Part D claims is suitable for our study because of two reasons. First, the cancer incidence rate is higher for older adults aged above 65 (DeSantis et al., 2019), which corresponds to the sample of most Medicare beneficiaries. Second, by 2022, close to 50 million of the more than 65 million Medicare beneficiaries opted for Part D plans.[3]

We leverage the variation in clinical trial timing of each new cancer drug across clinical trial sites to construct a staggered difference-in-difference (DID) research design, in which the treated physicians are those practicing in the same HRR as the clinical trial site of a new cancer drug and the control physicians are those never exposed to any clinical trials of that drug in their

3 https://www.kff.org/medicare/fact-sheet/an-overview-of-the-medicare-part-d-prescription-drug-benefit/

HRRs. Overall, we find that the exposure to clinical trials of new cancer drugs increases the likelihood that physicians prescribe these drugs by 0.18 percentage points, representing a 14% increase relative to the average prescribing rate. We substantiate that this result is consistent with localized knowledge spillover as, even within the same HRR, physicians practicing closer to clinical trial site of a new cancer drug increase their prescribing rates of that drug relative to the physicians practicing further away from the site.

We further show that there are heterogeneities in our results. First, the localized knowledge spillover depends on site characteristics. The localized knowledge spillover from clinical trial site to physicians is stronger when the trial site hosts the first author of pivotal trial, when the physicians are affiliated with trial sites, and when exposure to trials before 2014 already. Second, we find that localized knowledge spillovers from pre-FDA approval clinical trials are similar to that from post-FDA approval clinical trials, and this spillover effect is stronger when the trials post the trials results or get supported from other organizations. Third, localized knowledge spillover is stronger for Hematology-Oncology physicians, physicians graduating from a higher-ranked medical school and with more experienced physicians, and male physicians. These results suggest that the geographical proximity to leading researcher, organizational proximity and physician characteristics affect the localized knowledge spillover.

This study contributes to two strands of literature. The first strand of literature examines how physicians respond to scientific information. Particularly, there is a strand of studies examining how physician prescribing responds to the published results of clinical trials.[4] Earlier studies employ drug sales to measure physician prescriptions and examine how it responds to

4 We focus our review on the literature that examines the direct effect of clinical trial publication on physician prescribing. There is another strand of studies examining how clinical publication complement detailing to affect physician prescribing (Ching & Ishihara, 2010).

scientific information. They mostly confirm that the publication of clinical trials results of a drug promotes its sales, but the effects are heterogeneous across drugs (Azoulay, 2002; Slejko et al., 2018; Sood et al., 2014). Recent studies strengthen the identification by examining the publication of clinical trials only relevant to a group of patients. Olson & Yin (2021) show physicians increase their prescribing to children after there is a publication of pediatric studies. McKibbin (2023) shows physicians adopt off-label use of cancer drug after the publication of a positive and significant results from off-label use randomized controlled trials (RCTs). However, the above studies do not study the localized effect of scientific information on physician prescribing because access to medical publication is presumably universal across physicians. A notable exception is Agha & Molitor (2018). They employ the publications from a pivotal clinical trial of new cancer drug as the scientific information. They show that patients are more likely to be prescribed of those drugs when their physicians are geographically proximate to the first author of publications.

The second strand of literature examines geographical localization of knowledge spillover. Since the seminal work of Jaffe et al. (1993), there has been a number of studies using patent citations to examine localized knowledge spillovers (Balsmeier et al., 2023; Belenzon & Schankerman, 2013; Murata et al., 2014; Thompson, 2006). However, knowledge of different fields has different levels of explicit and tacit knowledge. Geography may play a different role in knowledge spillovers across fields. Thus, there are studies examining localized knowledge spillover beyond patent citation. Belenzon & Schankerman (2013) and Balsmeier et al. (2023) find that there is localized knowledge spillover for scientific knowledge, but the distance effect on scientific knowledge spillover is weaker than technological knowledge spillover. In a closer relationship to our work, Agha & Molitor (2018) show that there is localized knowledge spillover from the first author of pivotal clinical trial of new drug to physicians.

To the best of our knowledge, this paper is the first to show that physicians prescribing increases in response to exposure to nearby clinical trials. Our work contributes to the first literature by showing there is geographic localized knowledge produced by clinical trials that facilitates nearby physicians to prescribe new drug. Importantly, the localized knowledge produced by clinical trials is less publicly known, which is different from the public information studied before, such as publication on medical journals and label released by the FDA. We also identify several mechanisms, such as local presence of the first author of pivotal trial and physician-trial site affiliation, to facilitate the spillover of such localized less publicized knowledge. We extend the second literature by showing a novel localized knowledge spillover in medicine, which occurs between clinical trial sites and physicians.

The rest of the paper is organized as follows. Section 2 describes the background of new drug development, and the data used in our analysis. Section 3 describes the empirical model. Sections 4 presents empirical results. Section 5 concludes.

2. Background and Data

2.1 Drug Development

There are multiple phases through which a clinical trial sponsor obtains approval to bring a new drug to the market.[5]

Pre-approval trials: The sponsor performs tests for toxicity on animals, then files an Investigational New Drug (IND) application to the FDA including animal test results and a plan for human testing. After the IND application is reviewed by the FDA and a local institutional

5 Clinical trial sponsors are such as individuals, institutions, pharmaceutical companies, Federal agencies, or other organizations that are responsible for initiating, managing, or financing the clinical trial, but do not conduct the research.

review board (IRB), there are three phases to complete the clinical trial process before the sponsor can submit their new drug to the FDA for consideration to be sold on the market (FDA, 2023).

Phase I trials: Phase I trials emphasize safety, dosing schemes and side effects. Researchers usually recruit (typically 20 – 80) volunteers and give them specific interventions to determine what the drug's most frequent side effects are and how the drug is metabolized and excreted. This information guides the design of Phase II trials.

Phase II trials: If Phase I trials do not reveal unacceptable toxicity, Phase II trials begin and explore the effectiveness of the drug for a particular indication over a range of doses, and to assess short-term side effects. These studies typically involve a few dozen to about three hundred patients who have the target condition.

Phase III trials: If Phase II trials show the new drug works, researchers proceed to Phase III trials to test whether the new drug is better than the existing drugs. Phase III trials test the experimental product in larger groups of people (typically range from several hundred to about 3000 people). Some phase III trials are pivotal clinical trials, which usually involve rigorous methodologies, including randomized controlled trials and double-blind designs, to ensure the reliability of results. The data gathered from pivotal clinical trials are crucial for the FDA to determine whether the drug meets the necessary standards for approval. These trials assess not only the therapeutic benefits of the drug but also potential side effects, interactions, and overall impact on patients' quality of life.

New Drug Application (NDA): After receiving reasonable and expectable results from these trials, the sponsor will meet with the FDA and then formally submit an NDA for drug approval. Finally, the FDA will review the NDA, drug's professional labeling, and approve the application or issue a response letter. Providers can then prescribe this new drug in practice.

Phase IV trials: For most approved drugs, clinical trials are continued even after a product is on the market, as part of the post-marketing surveillance. The Phase IV trials aim to gather more information on side effects, risks, benefits, efficacy, and optimal use, or track its safety in general population. Phase IV trials might also test the treatment for other medical uses, different doses, or new combinations with other treatments. Even after FDA approval, early-phase (Phase I–III) trials often continue to explore new indications, dosing regimens, or patient populations (Grabowski et al., 2024; Ouimet et al., 2022; Skydel et al., 2019). Many post-approval studies are labeled Phase II because they test the drug in different diseases, combinations, or formulations. Thus, early-phase trials after approval reflect ongoing clinical development and label expansion, not incomplete approval. The whole stages of drug development and review process are shown in Figure 1.

All these clinical trials involve several to thousands of trial sites according to their research plans. These sites include hospitals, universities, doctors' office and community clinics (summarized by author according to the ClinicalTrials.gov, website: https://clinicaltrials.gov/), which are typically chosen by the study sponsor or contract research organizations (CROs) based on a methodical proves (Cramer, 2024). The choice of trial sites typically relates to their patient population availability, resources at the site, and data collection procedures (Dombernowsky et al., 2019). There is no evidence showing nearby physicians' prescribing behavior of new drug is a factor in choosing trial sites. In contrast, physicians practicing close to a trial site may be exposed to the clinical trials, for example through referring their patients to the clinical trials and being informed about the new drug.

2.2 Data and Summy Statistics

(1) Physician Prescription Data

We collect information about physicians and their prescribing of new cancer drugs using the Medicare Part D Prescribers - by Provider and Drug dataset provided by the Centers for Medicare & Medicaid Services (CMS).[6] This dataset also provides the National Provider Identifiers (NPI), address and specialty of physicians, drug prescribing decision, number of claims and number of Medicare beneficiaries of physicians. A caveat of this dataset is that there is a truncation issue. If a physician prescribes a type of drug for 10 or fewer claims, it is not included in this dataset. For example, if a physician prescribes a new cancer drug once over our sample period, our dataset cannot capture that new drug prescription. This issue would lead our estimate of new drug adoption to be conservative.

We collect this dataset for the period 2014-2019 and aggregate the data to physician-HRR-drug-year level. We employ the HRR as the aggregation level of location because HRR is widely used in previous research (Kilaru et al., 2015; Tang et al., 2016). There are 306 HRRs as defined by the Dartmouth Atlas of Health Care. An HRR can include 20 to 600 zip codes, with an average of over 200 zip code.[7]

(2) Physician Characteristics Data

Since not all physicians prescribe cancer drugs approved from 2014 to 2019, we select the top related specialties that prescribe those drugs. We include physicians specializing in Hematology, Hematology-Oncology, Medical Oncology and Gynecological Oncology. Also, we do not allow physicians to work in multiple HRRs or relocating during the sample period because we need to match each physician to a unique HRR for identifying the impacts of clinic trials

6 Data source: https://data.cms.gov/provider-summary-by-type-of-service/medicare-part-d-prescribers/medicare-part-d-prescribers-by-provider-and-drug

7 I match each physician's zip code with the corresponding HRR region using geographic data provided by the Missouri Census Data Center. URL: https://mcdc.missouri.edu, updated to October 2022.

exposure. This drops 94 physicians (less than 1%) of our sample physicians. As a result, we have 13,204 physicians in our sample, in which most of them belong to Hematology-Oncology (see Table 2).

(3) New Cancer Drugs and Clinical Trials Data

We collect the new drug list approved from 2014 to 2019 from FDA's Center for Drug Evaluation and Research (CDER) website.[8] Each year, CDER approves a wide range of 20–50 new drugs and biological products. To match the period of physician prescription data, we select the drugs with approval from 2014 to 2019, totally 258 drugs are included in which 38 of them are cancer drugs. We use 29 new cancer drugs in our empirical analysis because there are no prescription records for the other 9 drugs.

To obtain information about or the trials sites of those new cancer drugs, we use *ClinicalTrials.gov* provided by the U.S. National Library of Medicine, which documents detailly 510,397 (as September 2024) privately and publicly funded clinical trials conducted in all 50 states and in 221 counties.[9] For each new drug, we collect the information on which trial sites (and their corresponding HRR), trial phases and when it performs its clinical trials. Table 2 reports that sample contains clinical trials in all four phases with the majority of them Phase II trials. Also, we identify pivotal clinical trials from FDA label of drugs, and first author's city of pivotal clinical trials from PubMed website.[10] Table 1 present the information of new cancer drugs.

To determine whether physicians are affiliated with trial sites located within their Hospital Referral Region (HRR), we first utilize CMS Doctors and Clinicians data archive files from

8 Data source: https://www.fda.gov/drugs/development-approval-process-drugs/new-drugs-fda-cders-new-molecular-entities-and-new-therapeutic-biological-products
9 Data source: https://beta.clinicaltrials.gov/
10 Source: https://pubmed.ncbi.nlm.nih.gov/

Physician Compare dataset, which provide quarterly updates on physicians' affiliations with hospitals and other demographic characteristics from 2014 onwards (Beilfuss & Linde, 2021).[11] We merge this data with the physician prescription dataset by matching the unique NPI and year, thereby creating affiliation variables for each physician from 2014 to 2019. Next, we match the unique PAC ID (Provider, Enrollment, Chain, and Ownership System Associate Control ID) of the group practice where the physician works with the group practice PAC ID of the trial site, or the Medicare CCN (CMS Certification Number) of the hospital where the physician provides services with the hospital Medicare CCN of the trial site. This approach identifies physicians who are both geographically exposed to clinical trials and affiliated with trial sites.

2.3 Summary Statistics

The sample consists of 1,373,216 physicians-HRR-drug-year observations of 29 new cancer drugs from 2014-2019. Here, we take one cancer drug "Alunbrig" that was approved in 2017 to illustrate what information is contained in dataset. In 2017, Alunbrig was initially approved by the FDA as a prescription drug used to treat adults with non-small cell lung cancer (NSCLC). To date, Alunbrig has had 17 clinical trials in total. We exclude 5 trials from our empirical analysis because one of them began in 2016 and was documented as pre-FDA-approved trial and the other 4 clinical trials started in 2020. The remaining 12 clinical trials were conducted in 521 trial sites during 2014-2019. Among over 13,000 sample physicians, we identify 28 physicians from 24 HRR regions who prescribed the drug "Alunbrig" between 2017 and 2019. Among those 28 physicians, 15 of them are from 11 HRRs in which there was at least one active or completed clinical trial conducted for the drug "Alunbrig".

11 Data source: https://data.cms.gov/provider-data/archived-data/doctors-clinicians#archive-notice

The outcome variable is an indicator taking the value 1 if a physician prescribes a new cancer drug in a year and 0 otherwise. Table 2 reports that, on average, there is 1.13% probability that ample physicians prescribe a new cancer drug. The treatment variable is an indictor taking the value 1 if there has been a clinical trial of a new cancer drug conducted in the practicing HRR of our sample physicians. In other words, we define these physicians as exposed to clinical trials of the new cancer drug. Table 2 reports that, on average, there is a 58.2% probability to observe the sample physicians has been exposed to a clinical trial of sample 29 new cancer drugs. Since there are many research sites performing clinical trials, there is only a 1.9% probability to observe the sample physicians who have been exposed to a clinical trial conducted in a site hosting the leading author. Also, there is only 1.6% probability to observe sample physicians who are affiliated with the research sites that conducted the clinical trials.

The empirical analysis aims to identify the impacts of clinical trial exposure on physician prescribing of new cancer drugs. As descriptive evidence, Figure 2 depicts that there is a significant gap in the prescription rate of all new cancer drugs between exposed-to-clinical-trials physicians and non-exposed physicians, but this gap is gradually closing. To make prescription rates over time comparable and to avoid the potential heterogeneity of new cancer drugs, we then focus on a single drug "Lynparza", which is approved in 2014. Again, the exposed-to-clinical-trials physicians are more likely to prescribe "Lynparza" in the first few years after the approval. Then, the non-exposed physicians catch up their prescription rate in 2018, i.e. 4 years after the approval.

3. Empirical Model

To estimate the effect of clinical trial exposure on the physician prescribing, we exploit the variations in timing of exposure to clinical trials to identify the causal impact of clinical trials on physician prescribing behaviors. The treated physician in this analysis is the physicians working

in the same HRR as the trial sites conducting the clinic trials, whereas the control physicians are those that have never been exposed to any clinical trials. We employ a staggered DD approach based on the methodology developed by Callaway & Sant'Anna (2021). This approach is particularly suitable for our analysis as it accounts for the staggered timing across clinical trials. Specifically, we employ the following DD model:

$$Y_{ijdt} = \alpha * Trial_{jdt} + X_j * \beta + \eta_i + \eta_{dt} + \epsilon_{ijdt} \quad (1)$$

where Y_{ijdt} is an indicator that takes a value of 1 if physician i from HRR j prescribes new drug d in t years after drug d was approved.[12] The treatment variable $Trial_{jdt}$ turns on to 1 when at least one clinical trial of drug d had been conducted at the physician i's region j in year t, that is physician could be exposed to the clinical trial of that drug. For example, there are 19 registered clinical trials and 90 research sites about drug "Ibrance" in HRR region "56" (includes metropolitan areas in Los Angeles-Long Beach-Anaheim, CA, Oxnard-Thousand Oaks-Ventura, CA, and Riverside-San Bernardino-Ontario, CA) since 2017. Indicator $Trial_{jdt} = 1$ for drug "Ibrance" and HRR region "56" in year 2017, 2018 and 2019, and 0 otherwise. The coefficient α describes the rise in likelihood of a physician prescribing a new drug after being exposed to clinical trials.

The treatment variable $Trial_{jdt}$ is different from that used in Agha & Molitor (2018) which only exploit the exposure to clinical trials before the FDA approval. we also exploit the clinical trials after the FDA approval, such as Phase IV trials and some Phase I, II, III trials. Since clinical

12 Due to the Medicare part D prescribers dataset's construction, I could only observe the cases that aggregated records based on total claims are higher than 11.

trials span several years, some of them start before the FDA approval while the others in a physicians region start after the FDA approval. For example, a drug approved in 2015 with a trial started in 2014. A trial site in Albany could begin participating in the trial in 2017, thus $Trial_{jdt} = 1$ when $t \geq 2017$ for physicians in Albany. In the robustness checks section, we perform a robustness check only keeping the exposure to pre-FDA approval clinical trials, where the treatment variable will become $Trial_{jd}$ and only has the variations at HRR-drug level, and we also perform a robustness check with exposure to post-FDA approval clinical trials by adding "HRR-drug" fixed effect to get the pure effects of exposure to clinical trials.

We include a vector of HRR-level controls X_j. Following Agha & Molitor (2018), we include physicians η_i fixed effects (FEs) reflecting physicians' tendency to prescribe new drug and include drug-year η_{dt} FEs reflecting different drug-year shocks. Other possible common, clinical trial-related, unobserved random shocks are further described by the bivariate clustered standard errors at physician and drug level.

4. Empirical Results

We present the results of Equation 1 in Table 3. Panel A reports the main results and robustness checks. Panels B, C and D report the heterogeneities of results.

4.1 Main Results

Column 1 of Panel A reports that there is a 0.18 percentage points increase (p-value < 0.01) in the probability of prescribing a new drug when a physician is exposed to clinical trials of that drug. This increase corresponds to a 14% increase in the average prescription rate of the full sample (1.3% in Table 2). We interpret this result as evidence of localized knowledge spillover from clinical trial sites to nearby physicians, which in turn lead to new drug adoption.

To substantiate the interpretation, we construct an indicator for physicians practicing in the same county as the trial site. This indicator measures a closer distance between physicians and trial site as county is typically smaller than HRR. We then estimate Equation (1) using the indicator of physician exposing to clinic trials in their counties (Column 2) and the indicator of physician exposing to clinic trials in their HRR but not their county (Column 3).

The results report that physicians exposing clinical trials in their county significantly increases new cancer drug prescriptions by 0.16 percentage points (p-value < 0.01). However, physicians exposing clinical trials in their HRR but not their county do not significantly increase new drug prescriptions. This stark contrast suggests that geographic proximity to trial sites enhances the knowledge spillover to physicians learning about the new drug. These results are also consistent with literature that there is localized knowledge spillover in adopting new drug.

4.2 Robustness Checks

(1) Parallel Trend Assumption

The identifying assumption underlying the DID model is that physicians exposing to clinic trials and not exposing to clinic trials would have similar trends in prescribing new drug. To test the validity of this assumption of parallel trends, we apply an event student approach and estimate the following equation:

$$Y_{ijdt} = \sum_{k=-5}^{5} \alpha_k * 1(t - t_i^* = k) * Trial_{jdt} + \eta_i + \eta_{dt} + \epsilon_{ijdt} \quad (2)$$

The set of indicators $1(t - t_i^* = k)$ interacts with $Trial_{jdt}$ that equal to 1 for year t before and after exposure to drug d's clinical trials for physician i working in HRR j. We normalized

$\alpha_{k=-1} = 0$ as we interpret all coefficients α_k are the effects of exposure to clinical trials on the outcome variables relative to the year prior to the exposure, i.e. k = -1.

Figure 3 presents the results of event studies that examine the impact of clinical trials exposure on physician prescribing behaviors The coefficients for the years leading up to the clinical trials are relatively flat, indicating no significant pre-trends that could confound the treatment effects. Also, there is an abrupt change following an exposure to clinical trials. Over the first three years of exposure to clinical trials, there is a slight increase of 0.1-0.2 percentage points in new drugs prescriptions relative to physicians who are never exposed to clinical trials during the sample period. Relative to the pre-treatment means of 1.3 percentage points, we associate an exposure to clinical trials with an immediate 25% increase in new drugs prescription. After 2 years, the impact of an exposure to clinical trials on new drug prescription reached the peak and then diminishes to an insignificant level.

Further, even though the pre-trend tests support the assumption of parallel trends, recent literature suggests that such tests may suffer from low statistical power. Thus we implement the framework developed by Rambachan & Roth (2023) to address this concern. This approach assesses the robustness of estimates and confidence intervals by examining potential violations of the parallel trend assumption (see Appendix A.1 for details).

(2) Alternative Samples

A potential concern is that unobserved characteristics at the HRR level may confound the relationship between clinical trial exposure and physician prescribing behavior. Specifically, certain HRRs may serve as persistent hubs for clinical trial activity, creating distinctive healthcare environments that differ systematically from other regions. In these high-intensity trial regions, physicians may be better connected through professional networks, more receptive to innovation,

or have greater access to information about new drugs through channels unrelated to direct trial exposure. If these unobserved regional characteristics drive both the concentration of clinical trials and higher rates of new drug adoption, baseline estimates could overstate the causal effect of trial exposure itself.

To address this concern, we exclude HRRs with the highest concentration of clinical trial activity from the analysis. Specifically, we drop the top 1% of HRRs ranked by frequency of clinical trials conducted during the study period. By removing these high-intensity trial regions, we limit the analysis to areas with more moderate levels of trial activity, where confounding from persistent regional characteristics is likely less severe. This restriction tests whether the estimated treatment effect is driven primarily by a small number of exceptional regions or reflects a more generalizable relationship between trial exposure and prescribing behavior. Column 4 of Panel A in Table 3 presents result from this restricted sample. The coefficient in clinical trial exposure remains positive and statistically significant at 0.0008, indicating that exposure to trials continues to increase new drug prescription rates even after excluding the most trial-intensive regions. The magnitude of the effect is comparable to the baseline estimate of 0.0008, suggesting that the relationship is not driven solely by unobserved confounders in high-intensity trial hubs but reflects a broader pattern across diverse healthcare markets. To further verify that results are not sensitive to this particular threshold, we conduct additional robustness checks using alternative exclusion cutoffs (top 3%, 5%, 10%, and 25%) as well as a heterogeneity analysis estimating treatment effects separately across quintiles of HRR trial intensity. These analyses, reported in Appendix A.2, show that the coefficient attenuates progressively as more high-intensity regions are removed, declining from 0.0008 when excluding the top 1% to 0.0006 when excluding the top 3%, and to 0.0003 when excluding the top 5% or more. The effect becomes statistically insignificant at

conventional levels when the top 5% or more of HRRs is excluded. This pattern indicates that the treatment effect is stronger in regions with higher trial concentration, suggesting some degree of effect heterogeneity across different healthcare environments.

(3) Sample Matching

To ensure that the estimated effects of clinical trial exposure are not driven by pre-existing differences between exposed and non-exposed physicians, we employ sample matching methods to construct a comparison group with similar observable characteristics. This approach helps mitigate potential selection bias by creating a valid counterfactual for the treated physicians.

We carefully select matching covariates based on their potential relationship with both trial exposure and drug adoption outcomes. These covariates include physician characteristics such as specialty, years since graduation, gender, number of publications in PubMed and medical school ranking. We also incorporate geographic and market variables including metropolitan areas. Given concerns that treatment HRR regions may have fundamentally different healthcare environments than control regions, we additionally incorporate healthcare utilization variables from the Dartmouth Atlas DATA (2024) to ensure control units provide adequate counterfactuals. These variables include durable medical equipment reimbursements per enrollee (Parts A&B), age-sex-race adjusted HMO mortality rates, HMP mortality rates, total mortality rate, percentage of diabetic Medicare enrollees receiving eye exam, hemoglobin A1c testing or having annual ambulatory visit to a primary care clinician. All covariates are measured prior to the trial period to avoid post-treatment bias.

We apply 1:1 nearest-neighbor propensity score matching to pair each clinical trial exposure event occurring between 2014 and 2019 with a physician living in control HRR region for a drug. First, we estimate a logistic regression model on a panel of drug × physician

observations from both treated and control physicians, using all covariates to predict the probability of trial exposure. Using the predicted probabilities as propensity scores, we match each treated drug × physician observation to the untreated observation with the closest propensity score, employing a caliper of 0.05 standard deviations to avoid poor matches.

Table A.2 and Table A.4 shows the post-match diagnostics, confirming substantial improvement in covariate balance. Standardized mean differences across all covariates decreased from a pre-match at highest of 33% to below 3% post-match. Additionally, propensity score distributions show strong overlap between treated and matched control groups in Figure A.3, indicating that the matching procedure successfully created comparable treatment and control groups. Table 3 Panel A, Column 5 shows that the estimated effect of exposure to clinical trials remains stable at 0.0016 after implementing the matching procedure, confirming the robustness of the baseline results. To further test robustness and improve efficiency, we also implement alternative matching methods including radius matching, kernel matching, Mahalanobis distance matching, coarsened exact matching, and entropy balancing, with detailed results presented in Appendix A.3.

(4) Permutation Tests

We perform a placebo test by randomly assigning exposure to clinical trials to physicians to account for any potential omitted variable problem. Given the random data generation process, the false exposure to clinical trials variable should produce no significant estimate with a magnitude close to zero; otherwise, it would indicate a misspecification of the DD estimation. Specifically, we create a falsified treatment indicator by randomly shuffling the actual trial exposure assignment across physicians within the same time period, while maintaining the same proportion of treated and control observations as in the original data. This procedure preserves the

sample structure and timing but breaks the true link between trial exposure and physician characteristics or practice environments.

Under the null hypothesis of correct model specification, this placebo exposure variable should produce an estimate that is both statistically insignificant and close to zero in magnitude. A significant placebo estimate would suggest that the baseline results are driven by omitted variables correlated with the assignment mechanism rather than by actual trial exposure. To increase the statistical power and reliability of this test, we repeat the randomization procedure 500 times, each time re-estimating the difference-in-differences specification with the falsified treatment variable. Table 3 Column 6 of Panel A reports the mean coefficient across these 500 placebo regressions, which is approximately zero and statistically insignificant. This result provides reassuring evidence that the baseline treatment effect is unlikely to be an artifact of omitted variable bias. Furthermore, the full distribution of the 500 placebo estimates, presented in Appendix A.3, shows that the actual treatment effect lies well outside the range of estimates obtained under random assignment, further confirming the robustness of the main findings.

4.3 Heterogeneities

(1) Site Heterogeneity

First, we examine whether the localized knowledge spillover of clinical trial site depends on whether the proximate clinical trial site hosts the leading researcher of the clinical trial. Previous study shows that physician prescribing behavior depends on their proximity to the first author of a pivotal clinical trial (Agha & Molitor, 2018). This relationship affects how quickly and confidently physicians adopt new drug, as local connections and direct communication with the leading researcher can shape their perceptions and decisions.

In practice, we categorize the physician exposure to clinical trials into two groups, namely physician exposure to clinical trial where the site hosts the first author of the pivotal trial and physician exposure to clinical trial where the site does not host any first author. Columns 1-2 of Panel B in Table 3 shows that physicians exposed to clinical trials where the site hosts the first author demonstrate a statistically significant increase of 0.49 percentage points (p-value < 0.05) in the probability of prescribing the new drug, whereas the corresponding effect from exposing to clinical trials where the site does not host the first author is only 0.17 percentage points (p-value < 0.01). These findings support that the geographical proximity to the trial sites hosting the leading researcher disproportionally increase the localized knowledge spillover to physicians learning about the new drug.

Second, we examine whether the localized knowledge spillover of clinical trial site depends on whether the physician is affiliated with the proximate clinical trial site. Previous study shows that affiliation between hospitals and physician facilitates the knowledge spillover from hospitals to their affiliated physicians (Post et al., 2022). Affiliation with trial sites may affect physician prescribing behavior by improving their accessibility of drug information. Physicians employed by hospitals often benefit from access to advanced knowledge and positive peer effects, which may contribute to better patient care and increased likelihood of prescribing (Scott et al., 2017). Affiliated physicians typically share common information systems, adhere to common clinical guidelines and receive training with their hospitals, all of which could facilitate prescribing decisions. Expectedly, affiliation with trial sites promote physician prescribing behavior of new drugs.

Columns 3-4 of Panel B in Table 3 find that physicians increase their prescription rate by 0.35 percentage points (p-value < 0.05) when exposed to clinical trials from their affiliated trial

site, compared to the 0.17 percentage points (p-value < 0.01) observed among non-affiliated physicians. These findings suggest that the affiliation with trial site facilitates the localized knowledge spillover from the trial site to physicians learning about the new drug.

The final two columns of Panel B distinguish between trials that occurred before 2014 (earlier than the sample periods) versus those conducted in 2014 or later, to test whether a history of prior trial activity in a region influences the effect of subsequent trial exposure. Trials conducted in the region before 2014 generate an effect of 0.23 percentage points during the 2014-2019 study period, while trials began only during 2014-2019 produce a smaller effect of 0.12 percentage points. This pattern suggests that regions with established histories of testing particular drug classes or working with specific pharmaceutical sponsors may develop stronger channels for information diffusion or greater physician familiarity with trial processes. Alternatively, drugs with earlier regional trial activity may have already generated some awareness among local physicians, making them more receptive to prescribing these drugs once they receive approval. The persistent effect even for drugs with prior regional trial exposure indicates that trial activity during the study period continues to influence prescribing behavior above and beyond any legacy effects from historical trial presence.

(2) Trial Phase Heterogeneity

We estimate Equations (1) for the subsample of clinic trials at different phases and report the results in Table 3 Columns 1-2 of Panel C. The exposure to Phase I/II/III trials before FDA approve the drug provides physician knowledge about the drug's safety and efficacy in a targeted patient population. After the drug is approved by FDA, Phase IV trials are likely to add information, such as efficacy and side effects, about the drug use for a broader patient population, which is helpful for physician prescribing.

Column 1 reports that the effect of exposing to Phase I/II/III trials is 0.0016 (p-value < 0.01). Since the treatment in this case occurred before sample period of physician prescription, this result is estimated with a specification closer to (Agha & Molitor, 2018), i.e. $Y_{ijdt} = \alpha * Trial_{jd} + X_j * \beta + \eta_i + \eta_{dt} + \epsilon_{ijdt}$. Further, Column 2 reports that the effect of exposing to Phase IV trials is 0.0029 (p-value < 0.01). These results suggest both types of clinical trials provide information to nearby physicians about the new drugs and encourage them to prescribe them.

The next two columns examine whether trial results were publicly posted on clinical trial registries such as ClinicalTrials.gov, which became subject to enhanced reporting requirements during the study period. Trials with results posted publicly generate an effect of 0.0024 (p-value < 0.01), while trials without posted results produce a smaller effect of 0.0009 (p-value < 0.01). Although both coefficients are statistically significant, the magnitude for trials without posted results is significantly smaller, suggesting that public result dissemination may play some role in facilitating adoption.

The final two columns distinguish between trials supported by any other organization. Support may include funding, design, implementation, data analysis or reporting. Supported trials generate an effect of 0.0029 (p-value < 0.01), while non-industry trials produce a much smaller and insignificant effect of 0.0005 (p-value > 0.1). This nearly six-fold difference highlights the importance of institutional backing and resources in translating trial exposure into practice change. Trials with support from academic institutions, government agencies, or foundations may benefit from several advantages. First, these trials often involve prestigious research institutions with established reputations and stronger connections to local medical communities, lending credibility to the findings and facilitating information dissemination through institutional channels. Second,

organizationally supported trials may have greater resources for result dissemination activities such as academic conferences, publications in high-impact journals, and educational seminars. Third, trials with academic or government support may focus on clinically important questions that resonate more strongly with practicing physicians compared to narrower commercial objectives.

(3) Physician Heterogeneity

Panel D in Table 3 shows the impact of clinic trial exposure on physicians prescribing behavior by physician characteristics. To do so, we classify physicians according to their number of publications based on PubMed, specialty, medical school, years after graduation and gender. These characteristics are shown to determine the physician's prescribing behavior. Specifically, Hematology-oncology physicians, physicians graduating from top medical schools, older physicians and male physicians are faster to adopt new prescription drugs (Méndez et al., 2021).

The results in Columns 1–4 of the first row in Panel D indicate that the number of publications has no significant heterogeneous effect on physicians' prescribing behavior. Columns 5–6 show that, in sample, physicians specializing in Hematology-Oncology exhibit the largest increase in prescribing probability when exposed to clinical trials. In second row of Panel D, the results in Columns 1-2 show that physicians graduated from the Top 15 and non-Top 15 medical schools increase their likelihood to prescribe new drug by 0.0047 (p-value < 0.01) and 0.0017 (p-value < 0.01) percentage points when they are exposed to the clinic trial of that drug, respectively. Columns 3-4 show that physicians with more than 10 years' experience increase their likelihood to prescribe new drug by 0.0022 (p-value < 0.01) when they are exposed to the clinic trial of that drug. In contrast, physicians with less than 10 years of experience tend to reduce their prescribing of the new drug under similar exposure, possibly because they are more cautious about adopting

new treatments, have less familiarity and autonomy in prescribing decisions, and prefer to rely on well-established therapies until more post-approval evidence becomes available. Columns 5-6 find that male physicians slightly increase their likelihood of prescribing new drug more than female physician when they are exposed to a clinic trial of that drug.

Overall, the localized knowledge spillover from clinical trial site to physicians is heterogeneous across physicians. The spillover is stronger for Hematology-Oncology physicians, physicians from a higher-ranked medical school, more experienced physicians and male physicians. It suggests that the proximity to clinical trial sites supports some physicians, who are typically slower in new drug adoption, to adopt new drug.

5. Conclusion

This study examines the effects of exposure to clinical trials on physician prescribing decisions. We find that when a physician is exposed to a nearby clinical trial of a new cancer drug, it increases the likelihood of prescribing that drug after FDA approval for 0.18 percentage points, constituting a 14% rise relative to the average prescription rate for new cancer drugs of sample. Our result is also consistent with localized knowledge spillover from clinical trial sites to nearby physicians as the proximity between clinical trial sites and physician plays an important role in driving our result. Moreover, the relationship between trial exposure and prescribing behavior exhibits substantial heterogeneity across multiple dimensions. The effects are strongest when trial sites host the first author of pivotal trials, when physicians are affiliated with trial sites, and when the sites have a history of conducting clinical trials, highlighting the critical importance of investigator prominence and institutional connections in mediating knowledge transfer. Hematology-Oncology, male physicians, graduates of top-ranked medical schools, and those with greater clinical experience respond more strongly to trial exposure, suggesting that academic

engagement and professional networks amplify the impact of geographic proximity. The findings also reveal that trial characteristics matter: Phase IV trials generate larger effects than early-phase trials, trials with publicly posted results produce stronger responses than those without, and trials with organizational support from academic institutions, government agencies, or foundations demonstrate substantially larger impacts than unsupported trials.

Our results highlight the policy implications of increasing geographical access to clinical trial sites to mitigate health inequity across space. Improving geographical access not only will promote the participation of clinical trial that directly benefits the participants, but it also promotes the prescription of new drug by nearby physicians that expands the potential population of patients benefiting from new drugs.

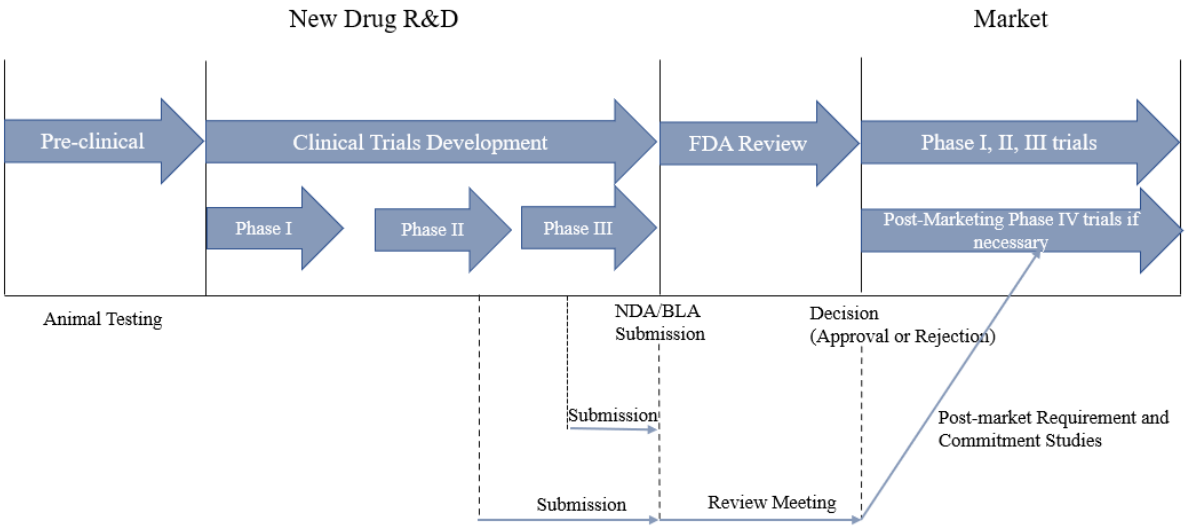


Figure 1. Stages of Drug Development and Review

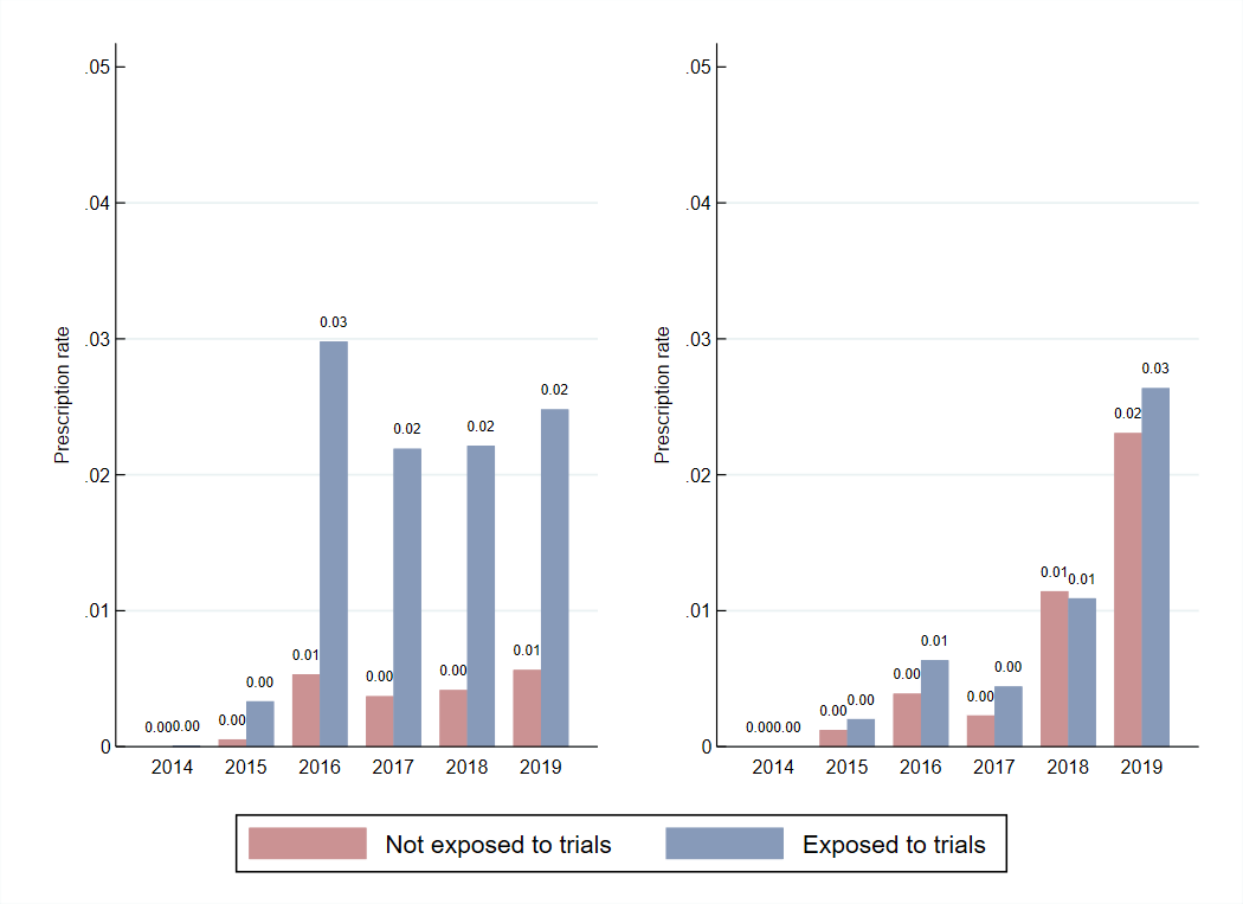


Figure 2. Prescription Rate of Cancer Drugs Over Time

Notes: Left figure includes all the new cancer drugs and right figure only includes one drug "Lynparza" (approved in 2014) as an example.

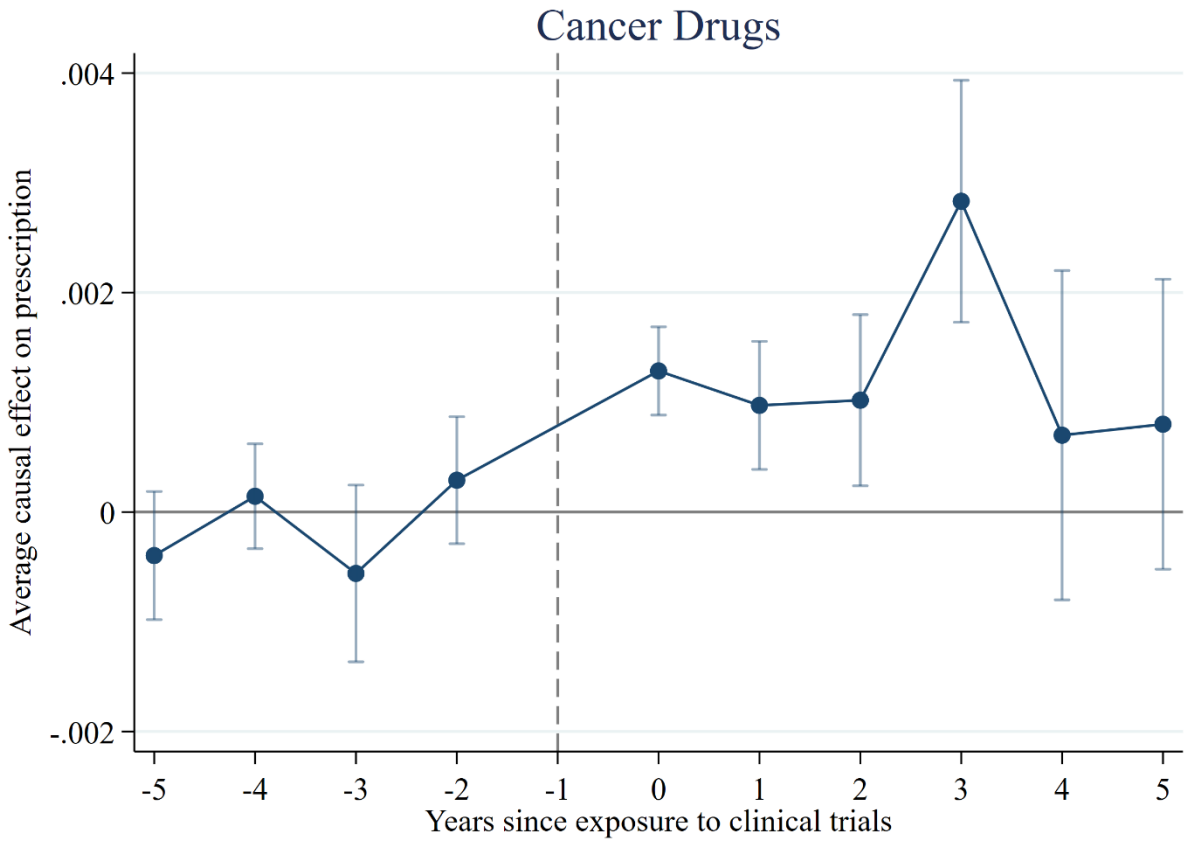


Figure 3. Dynamic Effects of Clinical Trial Exposure on New Cancer Drug Prescribing

Notes: The figures show the event-study estimates using a stacked event study model. For each cohort, the control group includes only physicians who are never exposed to clinical trials during the sample period. The outcome used in Figure 3 is dummy variable for drug prescription (zero for not prescribing). The x-axis measures years relative to the first year of clinical trial exposure in a physician's HRR, with year -1 serving as the omitted reference period. The y-axis shows the estimated coefficient on trial exposure from a difference-in-differences specification that includes leads and lags of the treatment indicator. Point estimates are shown as dots, and vertical bars represent 95% confidence intervals based on standard errors clustered at the drug-physician level. The vertical dashed line at year -1 marks the reference period immediately before trial exposure begins. The pattern of coefficients provides evidence on pre-treatment trends (years -5 to -1) and the dynamic evolution of treatment effects after exposure (years 0 to 5). Pre-treatment coefficients near zero and statistically insignificant support the parallel trends assumption underlying the difference-in-differences design. Post-treatment coefficients show the time path of the treatment effect, indicating how physicians' prescribing behavior evolves following exposure to clinical trials in their region.

Table 1. New Cancer Drugs 2014-19 and their Pivotal Clinical Trials

Drug Name	Approved Year	Indication	Pivotal Clinical Trails				
			Trial Sites	Patients Enrolled	Publication Year	Number of Authors	First Author City
Cyramza	2014	Stomach cancer	119	355	2014	24	Boston
Lynparza	2014	Ovarian cancer	13	298	2015	16	Isreal
Sylvant	2014	Lymph nodes	38	79	2014	22	Little Rock
Zydelig	2014	Blood cancer	90	220	2014	28	New York
Zykadia	2014	Lung cancer		163	2014	21	Boston
Alecensa*	2015	Lung cancer	56	253	2016	18	Orange
Ibrance	2015	Breast cancer	50	165	2015	18	Los Angeles
Lenvima	2015	DTC		392	2015	19	Foreign
Lonsurf	2015	Colorectal cancer		800	2015	24	Boston
Odomzo	2015	Cell carcinoma	58	230	2015	23	Houston
Portrazza	2015	Lung cancer	184	1093	2015	20	Manchester
Tagrisso	2015	Lung cancer		411	2016	5	Taipei
Axumin	2016	Prostate cancer					
Rubraca	2016	Ovarian cancer	87	564	2017	34	Houston
Tecentriq*	2016	Bladder cancer	77	310	2016	31	New York
Alunbrig	2017	Lung cancer		222	2017	20	South Korea
Bavencio	2017	Cell carcinoma	35	88	2016	18	New Brunswick
Imfinzi	2017	Carcinoma	60	182	2017	16	London
Kisqali	2017	Breast cancer	223	668	2016	37	Houston
Nerlynx	2017	Breast cancer	495	2840	2016	30	Australia
Verzenio	2017	Breast cancer	142	669	2017	18	Stanford
Xermelo	2017	Diarrhea		90	2018	18	Berlin
Zejula	2017	Recurrent epithelial ovarian,		733	2019		Foreign

(Continue)

Drug Name	Approved Year	Indication	Pivotal Clinical Trails				
			Trial Sites	Patients Enrolled	Publication Year	Number of Authors	First Author City
Erleada	2018	Prostate cancer	332	1207	2018	18	Boston
Libtayo	2018	Advanced cutaneous squamous cell carcinoma(CSCC)	163	26	2018	37	Houston
Lorbrena	2018	Lung cancer	104	296	2020	14	Boston
Lutathera	2018	Cancer	41	229	2021	20	Tampa
Talzenna	2018	Breast cancer	145	431	2018	18	Houston
Vitrakvi	2018	Cancer (biomaker)		176	2018	38	New York
Vizimpro	2018	Lung cancer		452	2021	4	San Diego
Balversa	2019	Bladder cancer		69			
Brukinsa	2019	Blood cancer		86	2020		Brukinsa
Enhertu	2019	Breast cancer		234	2019	23	New York
Nubeqa	2019	Prostate cancer		1509		15	France
Padcev	2019	Bladder cancer		125	2021	20	Seattle
Piqray	2019	Breast cancer		572	2019	20	Boston
Rozlytrek	2019	non-small cell lung cancer (NSCLC)		355	2020	38	Aurora

Table 2. Summary Statistics

Variables	Obs.	Mean	SD	Min	Max
Physician-Drug-year level					
Indicator for prescription new drugs	1,373,216	0.013	0.115	0	1
Indicator for exposure to clinical trials	1,373,216	0.582	0.493	0	1
Indicator for first-author region	1,373,216	0.019	0.135	0	1
Indicator for being affiliated with research sites	1,373,216	0.016	0.124	0	1
Indicator for same county with research sites	1,373,216	0.411	0.492	0	1
Physician level					
Number of physicians	13,204				
Number of physicians - Hematology	923				
Number of physicians - Hematology-Oncology	8,504				
Number of physicians - Medical Oncology	3,695				
Number of physicians - Gynecological Oncology	926				
Clinical trial level					
Number of clinical trials	2,576				
Number of clinical trials - Phase I	721				
Number of clinical trials - Phase II	1,417				
Number of clinical trials - Phase III	332				
Number of clinical trials - Phase IV	12				

Notes: The total number of physicians from those four specialties is larger than the total number of sample physicians because some physicians declare more than one specialty. The total number of clinical trials from those four phases is fewer than the total number of sample clinical trials because some trials do not list their phases.

Table 3. Effects of Clinical Trial Exposure on New Cancer Drug Prescribing: Main Results and Heterogeneity Analysis

	(1)	(2)	(3)	(4)	(5)	(6)
Panel A		Same County with Trial Sites			Robustness	
Main Results	Benchmark	Yes	No	Excl.Top 1% HRRs	Sample Matching	Permutation
Trial	0.0018***	0.0016***	-0.0001	0.0008***	0.0016***	0.0000
	(0.0003)	(0.0004)	(0.0003)	(0.0003)	(0.0042)	(0.0002)
Observations	1,373,216	1,373,216	1,373,216	1,196,104	1,373,216	
Panel B	Trial Sites w/ First Author		Affiliate with Trial Sites		Trial Sites Before 2014	
Site Heterogeneities	Yes	No	Yes	No	Yes	No
Trial	0.0049**	0.0017***	0.0035**	0.0017***	0.0023***	0.0012***
	(0.0013)	(0.0003)	(0.0018)	(0.0028)	(0.0037)	(0.0034)
Observations	1,373,216	1,373,216	1,373,216	1,373,216	1,373,216	1,373,216
Panel C	Phase of Trials		Trials with Results Posted		Trials Supported by Others	
Trials Heterogeneities	Phase I/II/III	Phase IV	Yes	No	Yes	No
Trial	0.0016***	0.0029***	0.0024***	0.0009***	0.0029***	0.0005
	(0.0003)	(0.0008)	(0.0003)	(0.0003)	(0.0003)	(0.0003)
Observations	1,373,216	1,373,216	1,373,216	1,373,216	1,373,216	1,373,216
Panel D		Academic Publications			Specialty	
Physicians Heterogeneities	< 10	[10,50]	[50,100]	>100	Hematology-Oncology	Medical Oncology
Trial	-0.0040	0.0020	0.0044	0.0039	0.0046***	0.0019***
	(0.0042)	(0.0014)	(0.0042)	(0.0041)	(0.0004)	(0.0006)
Observations	1,373,216	1,373,216	1,373,216	1,373,216	1,373,216	1,373,216
	Sch Ranking		Years after Graduation		Gender	
	Top 15	> 15	<10	≥10	Male	Female
Trial	0.0047***	0.0017***	-0.0078***	0.0022***	0.0021***	0.0020***
	(0.0017)	(0.0003)	(0.0008)	(0.0003)	(0.0004)	(0.0005)
Observations	1,373,216	1,373,216	1,373,216	1,373,216	1,194,189	1,194,189
Physician FEs	Yes	Yes	Yes	Yes	Yes	Yes
Drug-year FEs	Yes	Yes	Yes	Yes	Yes	Yes

Notes: This table presents difference-in-differences estimates of the effect of clinical trial exposure on the likelihood that physicians prescribe new cancer drugs. The dependent variable equals one if a physician prescribed a new drug in a given year and zero otherwise. Panel A reports main results and robustness checks. Column 1 presents the baseline specification. Column 2 restricts the sample to physicians practicing in the same county as clinical trial sites, while Column 3 restricts physicians in counties without trial sites. Column 4 excludes HRRs in the top 1% of the trial intensity distribution as a test for confounding from high-trial-activity regions. Column 5 reports estimate using 1:1 nearest-neighbor propensity score matching to balance observable characteristics between treated and control physicians. Column 6 presents the mean coefficient from 500 placebo regressions in which trial exposure is randomly reassigned across physicians. Panel B examines heterogeneity in treatment effects by trial timing and site characteristics. Panel C explores heterogeneity by trial phase (Phase I/II/III versus Phase IV) and whether trial results were publicly posted. Panel D investigates heterogeneity by physician characteristics, including academic publication records, specialty (hematology-oncology versus medical oncology), medical school ranking, years since graduation, and gender. All specifications include physician fixed effects and drug-year fixed effects. Standard errors in parentheses are clustered at the drug-physician level. *** $p<0.01$, ** $p<0.05$, * $p<0.1$.

Appendix

A.1 Addressing Potential Violations of Parallel Trends

Rambachan & Roth (2023) proposed an approach for robust inference and sensitivity analysis tools for DiD when parallel trends may be violated and study their impacts on the point estimates and confidence intervals of interest. Specifically, we adopt "relative magnitudes" restriction the main robustness test of Rambachan and Roth (2023), which allows the violation of parallel trends to be no more than M times larger than the maximum pre-treatment violation of parallel trends. Estimates of the confidence interval for the average effect between first period post event α_0 and last period post event α_5 in Equation (2) are shown in Figure A.1. We observe that the "breakdown value" for a significant effect is $\bar{M} = 1$, meaning that the significance of the average post-treatment estimate is robust to allowing for violations of parallel trends up to the maximum violation in the pre-treatment period.

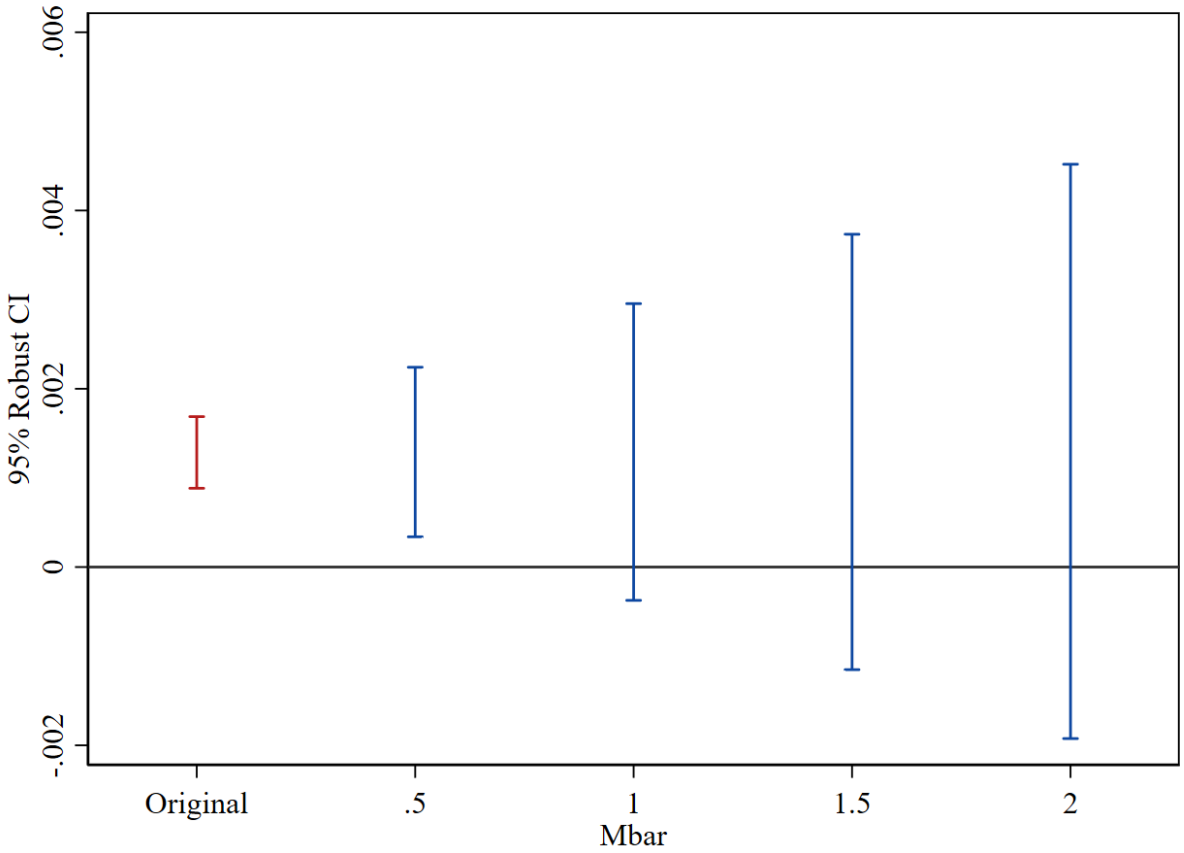


Figure A.1 Sensitivity Analysis on Average Effects using Assumptions on the Relative Magnitude

A.2 Alternative Samples

This appendix presents additional robustness checks that test whether the main results are sensitive to the inclusion of high-intensity clinical trial regions. As discussed in the main text, a concern is that HRRs with concentrated trial activity may have unobserved characteristics that independently drive new drug adoption. For instance, regions that repeatedly host clinical trials may develop specialized infrastructure, cultivate stronger relationships between academic medical centers and community physicians, or attract patient populations that are systematically different in their healthcare-seeking behavior or disease severity. These unobserved regional characteristics could create spurious correlations between trial exposure and prescribing patterns if they simultaneously attract clinical trials and promote faster adoption of new drugs through channels unrelated to trial activity itself. We address this concern through two complementary approaches: varying the exclusion threshold for high-trial-intensity HRRs and estimating heterogeneous treatment effects across different levels of regional trial intensity.

Table A.1 reports estimate of the clinical trial exposure effect under different sample restrictions. Each column corresponds to a specification that excludes HRRs above a specified percentile of total trial activity during the study period, where trial intensity is measured as the cumulative number of unique clinical trials conducted in each HRR between 2014 and 2019. Column 1 reproduces the baseline estimate using the full sample for comparison, which includes all 304 HRRs in the dataset. Columns 2 through 6 present results excluding the top 1%, 3%, 5%, 10%, and 25% of HRRs by trial intensity, respectively, which removes 4, 10, 16, 31, and 76 HRRs from the analysis.

The distribution of trial intensity across HRRs exhibits substantial concentration in a small number of regions. The full sample shows substantial variation in trial activity, with excluding

HRRs in the top percentiles hosting considerably more trials than the average region. As increasingly trial-intensive regions are removed from the sample, the estimated treatment effect attenuates in both magnitude and statistical significance. The baseline coefficient of 0.0018 (significant at the 1% level) decreases to 0.0008 when excluding the top 1% of HRRs, further declines to 0.0006 when excluding the top 3%, and becomes statistically insignificant at conventional levels when excluding the top 5% or more of regions.

This pattern of attenuation suggests that the relationship between clinical trial exposure and new drug adoption is stronger in regions with higher overall trial intensity. Several interpretations are possible. First, high-intensity trial regions may have unobserved characteristics such as stronger physician networks, greater receptivity to innovation, or better information diffusion mechanisms that amplify the effect of trial exposure on prescribing behavior. Second, physicians in these regions may have more direct or indirect connections to trial activities, making trial-related information more salient and actionable. Third, the concentration of effects in high-trial regions could reflect threshold effects, where trial exposure influences prescribing behavior only when physicians are embedded in healthcare environments with sufficient trial infrastructure and culture.

The substantial reduction in the coefficient magnitude and loss of statistical significance when excluding the top 5% to 25% of HRRs warrants careful interpretation. On one hand, this sensitivity indicates that the average treatment effect estimated in the full sample is partly driven by regions with exceptionally high trial activity, which may limit the generalizability of the findings to more typical healthcare markets. On the other hand, approximately 95% of HRRs remain in the sample even after excluding the top 5%, suggesting that the estimated effects in the restricted samples may lack statistical power due to reduced variation in trial exposure rather than

reflecting a true absence of treatment effects in moderate-intensity regions. The loss of statistical significance as more regions are excluded could therefore reflect both genuine effect heterogeneity and declining precision from smaller sample sizes and reduced treatment variation.

Table A.1 Robustness to Exclusion of High-Intensity Trial Regions

	(1)	(2)	(3)	(4)	(5)	(6)
	Full sample	Exclude Top 1%	Exclude Top 3%	Exclude Top 5%	Exclude Top 10%	Exclude Top 25%
Trials	0.0018***	0.0008***	0.0006*	0.0003	0.0003	0.0001
	(0.0003)	(0.0003)	(0.0003)	(0.0003)	(0.0004)	(0.0006)
Observations	1,373,216	1,196,104	1,056,640	952,952	751,192	413,192
Number of HRRs	304	300	294	288	273	228
Number of Physicians	13204	11501	10160	9163	7223	3973
HRRs Excluded	0	4	10	16	31	76
Mean Trials in Excluded HRRs	14244.35	9716.22	7850.01	6802.04	4982.80	2642.30

Notes: This table reports difference-in-differences estimates of the effect of clinical trial exposure on new drug prescribing under alternative sample restrictions. Column 1 presents baseline specification using the full sample of 306 HRRs. Columns 2-6 sequentially exclude HRRs in the top 1%, 3%, 5%, 10%, and 25% of the distribution of total clinical trials conducted during 2014-2019. All specifications include physician, drug, and year fixed effects. Standard errors (in parentheses) are clustered at the HRR level. *** p<0.01, ** p<0.05, * p<0.1.

A.3 Sample Matching

Before estimating the average treatment effect on the treated (ATT), it is necessary to confirm that observed covariates are balanced between the treatment (physicians exposed to a clinical trial) and control groups. Initial diagnostic analysis, presented in Table A.2, reveals significant pre-match imbalances. The Standardized % Bias exceeded the 20% threshold for several key covariates, most notably for Total Mortality Rate (-33.2%), Non-HMO Mortality Rate (-30.3%), and Durable Medical Equipment Reimbursement Per Enrollee (32.2%). These large standardized differences, alongside highly significant t-test values (p-value < 0.01) for most variables, motivate the use of Propensity Score Matching (PSM) to construct a counterfactual control group and improve comparability. The propensity score, representing the conditional probability of receiving treatment, is estimated using a logit model. The validity of the model specification is confirmed by satisfying the balancing property test across blocks of the propensity score. The Estimated Propensity Score Histogram (Figure A.2) demonstrated adequate common support between the Treatment and Control distributions prior to matching, with substantial overlap across the primary range (0.4 to 1.0), ensuring that the matching process could proceed with minimal loss of treated observations. To ensure the robustness of the ATT estimate, six distinct matching algorithms are implemented. As summarized in Table A.3, all methods successfully match 823,882 treated observations to 342,002 matched control observations. The efficacy of the matching process in reducing bias is visually demonstrated in Figure A.3, which plots the standardized percent bias across covariates. The figure clearly shows the substantial reduction in bias, with the Matched points clustering tightly around the zero line, confirming that no matched covariate exceeded an absolute standardized percent bias of 10%.

Detailed covariate balance diagnostics, presented in Table A.4, confirm the superior balancing properties of several methods. Entropy Balancing (EB) achieves the most precise balance, with all post-match Standardized Mean Differences (SMD) registering 0.0. The Kernel Matching (b=0.06) and Radius Matching (0.05 SD) methods also perform exceptionally well, with the majority of SMDs falling below 0.5. Furthermore, the $V(T)/V(C)$ ratios from the initial balance check (Table A.2, Column 6) are tightly centered around 1.0 after matching, ranging from 0.89 to 1.29, indicating good distributional balance. The core objective of this multi-methodological approach is to verify the consistency of the ATT estimates. As shown in Table A.3, the ATT estimates are positive, statistically significant (p-value < 0.01), and remarkably stable across all six matching algorithms, exhibiting a narrow range from 0.0015 (Nearest-Neighbor and Kernel) to 0.0018 (Mahalanobis Distance). This high consistency and significance across methods confirm that the observed increased adoption of new drugs because of exposure to clinical trials, is robust to the chosen balancing technique, strengthening the causal inference and confirming that the effect is independent of observed baseline characteristics.

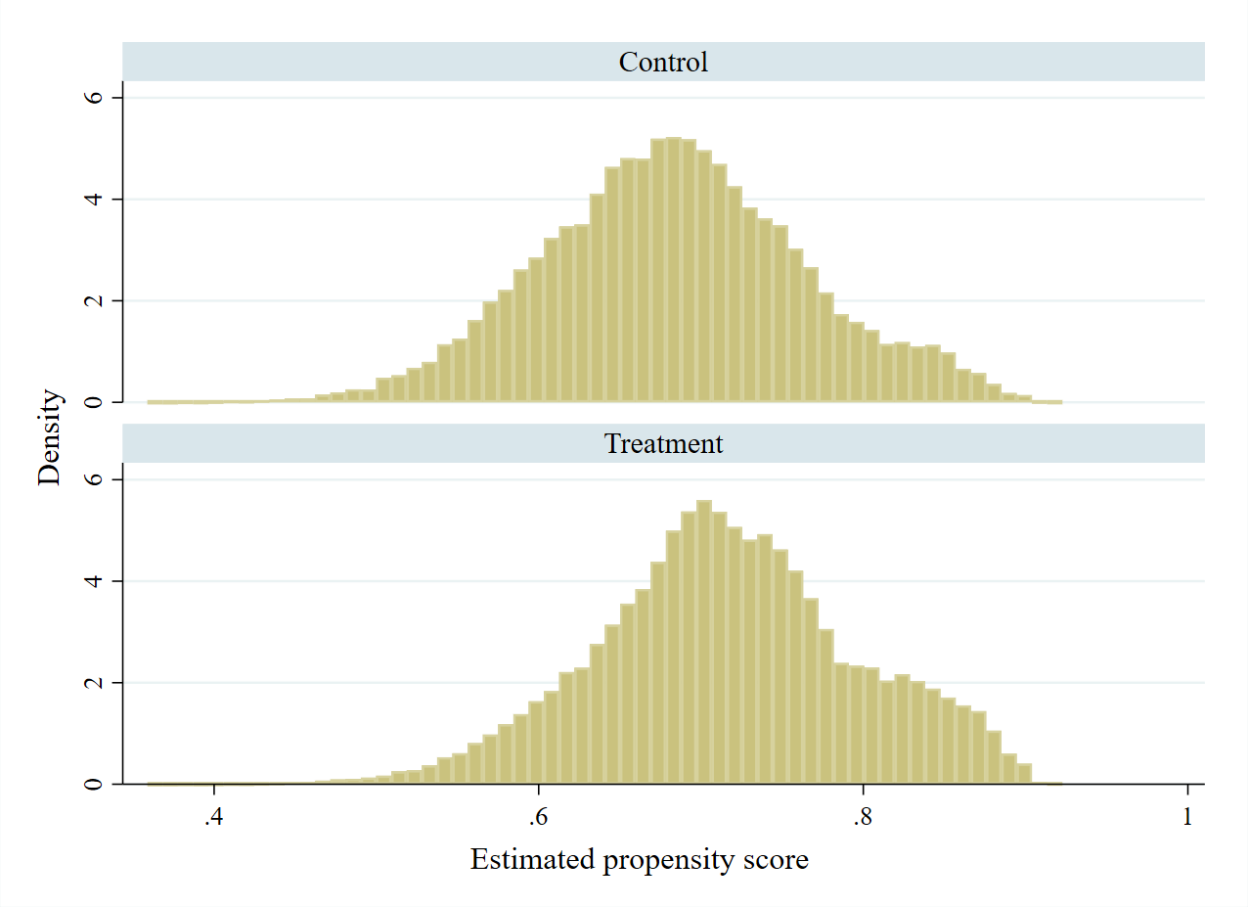


Figure A.2 Histogram of Estimated Propensity Scores by Treatment Group Before Matching

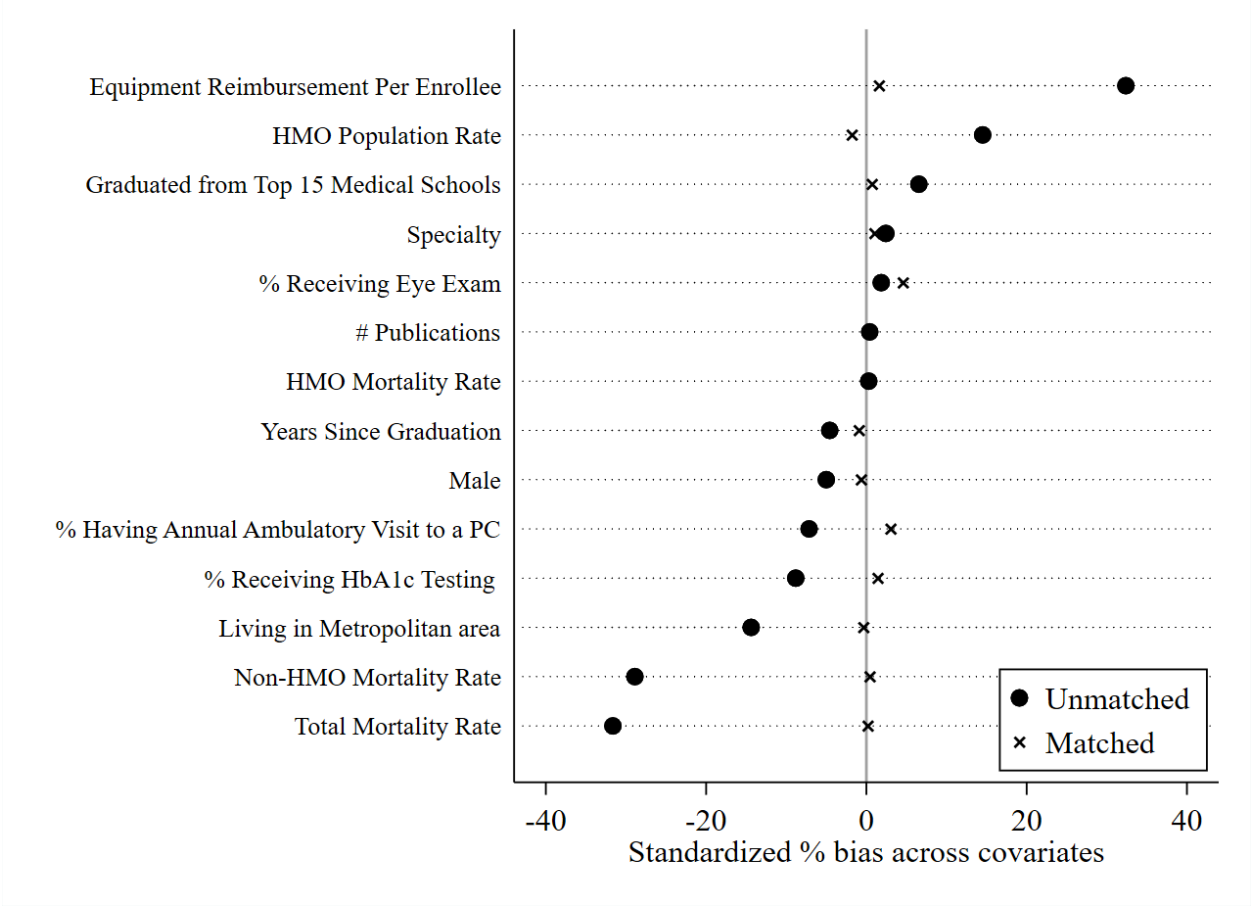


Figure A.3 Standardized Mean Differences for Covariates Before and After Nearest-Neighbor PSM Matching

Table A.2 Covariate Balance Between Treatment and Control Groups Before Matching

	(1)	(2)	(3)	(4)	(5)	(6)
	Mean			t-test		$V(T) / V(C)$
	Treatment	control	% Bias	t	$P > \|t\|$	
Specificity	3.058	3.042	2.1	11.01	0.000	1.06*
Years since Graduation	25.766	26.280	-4.4	-21.98	0.000	1.00
Male	1.663	1.684	-4.6	-22.73	0.000	1.03*
Graduated from Top 15 Medical Schools	0.033	0.024	5.9	30.78	0.000	.
Living in Metropolitan area	1.040	1.075	-14.8	-83.15	0.000	0.56*
Number of Publications	327.99	304.39	0.3	1.67	0.095	1.04*
Durable Medical Equipment Reimbursement Per Enrollee	11603	10531	32.2	168.19	0.000	1.29*
HMO Mortality Rate	-1.067	-2.574	0.4	2.17	0.000	0.42*
HMO Population Rate	0.372	0.351	16.1	87.11	0.000	0.93*
Non-HMO Mortality Rate	0.042	0.043	-30.3	-163.92	0.000	0.92*
Total Mortality Rate	0.041	0.042	-33.2	-179.67	0.000	0.90*
% of Diabetic Medicare Enrollees Receiving Eye Exam	68.035	67.935	2.3	12.13	0.000	1.05*
% of Diabetic Medicare Enrollees Receiving HbA1c Testing	86.834	87.122	-9.0	-48.68	0.000	0.89*
% of Medicare Enrollees Having Annual Ambulatory Visit to a Primary Care Clinician	64.787	65.15	-7.0	-36.97	0.000	1.08*

Note: * means the variance ratio outside [1.00; 1.00].

Table A.3 Summary of Matched Samples and Treatment Effects among Multiple Matching Methods

	(1)	(2)	(3)	(4)	(5)
Matching Method	Treated Obs	Matched Control Obs	ATT	Std. Error	p-value
Nearest-Neighbor PSM	823,882	342,002	0.0015	0.0003	< 0.01
Radius Matching (0.05 SD)	823,882	342,002	0.0017	0.0003	< 0.01
Kernel Matching (b=0.06)	823,882	342,002	0.0015	0.0002	< 0.01
Mahalanobis Distance	823,882	342,002	0.0018	0.0003	< 0.01
Coarsened Exact Matching	823,882	342,002	0.0017	0.0003	< 0.01
Entropy Balancing	823,882	342,002	0.0016	0.0003	< 0.01

Table A.4 Standardized Mean Differences (SMD, %Bias) and Covariate Balance Diagnostics After Matching

	(1)	(2)	(3)	(4)	(5)	(6)
Covariate	Nearest-Neighbor	Radius	Kernel	Mahalanobis	CEM	Entropy Balancing
Specificity	1.0	0.2	0.1	0.8	-2.0	0.0
Years since Graduation	-0.9	0.1	0.0	-0.2	0.4	0.0
Male	-0.7	0.3	-0.1	-0.1	0.6	0.0
Graduated from Top 15 Medical Schools	0.7	-0.2	0.1	0.5	-0.6	0.0
Living in Metropolitan area	-0.4	0.1	0.0	-0.4	0.2	0.0
Number of Publications	0.3	0.5	0.3	0.9	-0.3	0.0
Durable Medical Equipment Reimbursement Per Enrollee	1.6	1.2	0.8	-0.6	-0.3	0.0
HMO Mortality Rate	0.1	0.0	0.0	0.1	-0.0	0.0
HMO Population Rate	-1.8	-0.3	-0.2	0.2	-0.2	0.0
Non-HMO Mortality Rate	0.4	0.2	0.1	-0.3	0.3	0.0
Total Mortality Rate	0.2	0.1	0.0	0.1	0.4	0.0
% of Diabetic Medicare Enrollees Receiving Eye Exam	4.6	1.0	0.5	-0.7	-0.3	0.0
% of Diabetic Medicare Enrollees Receiving HbA1c Testing	1.4	0.2	0.1	0.4	0.8	0.0
% of Medicare Enrollees Having Annual Ambulatory Visit to a Primary Care Clinician	3.0	0.4	0.2	-0.5	0.7	0.0

A.4 Permutation Test

We randomly assign exposure to clinical trials to physicians and estimate the DiD model. I repeat the procedure for 500 time. The distribution of placebo estimates (the dots) is located around zero (Mean = 0.0000011 and standard deviation = 0.00019). The benchmark estimation (red vertical line) is located outside the entire distribution of the placebo estimates.

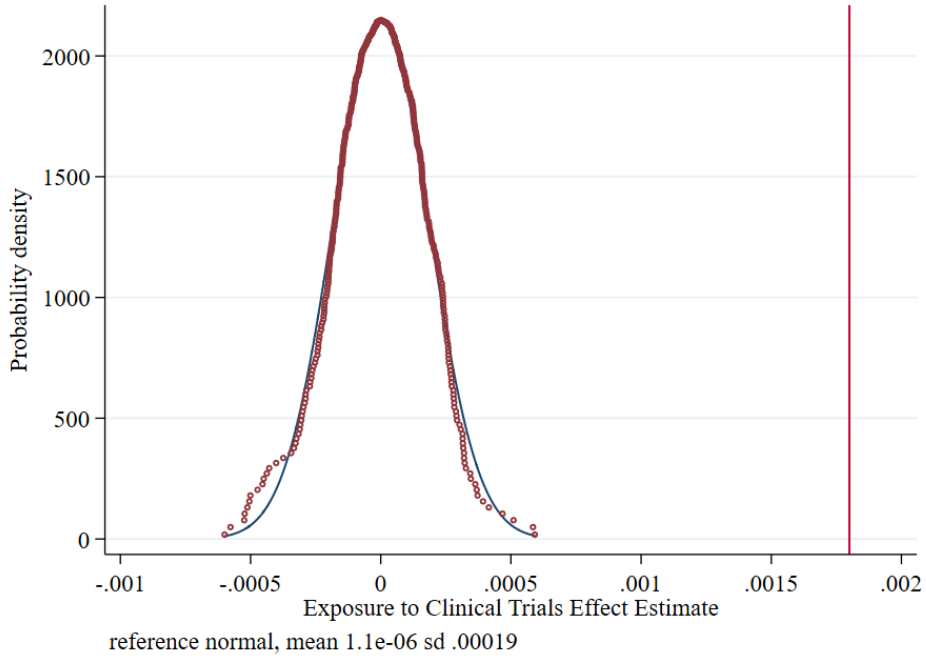


Figure.4 Placebo Test Results

Reference

Agha, L., & Molitor, D. (2018). The Local Influence of Pioneer Investigators on Technology Adoption: Evidence from New Cancer Drugs. *The Review of Economics and Statistics*, *100*(1), 29–44. https://doi.org/10.1162/REST_a_00670

Azoulay, P. (2002). Do Pharmaceutical Sales Respond to Scientific Evidence? *Journal of Economics & Management Strategy*, *11*(4), 551–594. https://doi.org/10.1111/j.1430-9134.2002.00551.x

Balsmeier, B., Fleming, L., & Lück, S. (2023). Isolating Personal Knowledge Spillovers: Coinventor Deaths and Spatial Citation Differentials. *American Economic Review: Insights*, *5*(1), 21–34. https://doi.org/10.1257/aeri.20210275

Belenzon, S., & Schankerman, M. (2013). Spreading the Word: Geography, Policy, and Knowledge Spillovers. *The Review of Economics and Statistics*, *95*(3), 884–903. https://doi.org/10.1162/REST_a_00334

Callaway, B., & Sant'Anna, P. H. C. (2021). Difference-in-Differences with multiple time periods. *Journal of Econometrics*, *225*(2), 200–230. https://doi.org/10.1016/j.jeconom.2020.12.001

Ching, A., & Ishihara, M. (2010). The effects of detailing on prescribing decisions under quality uncertainty. *QME*, *8*(2), 123–165. https://doi.org/10.1007/s11129-010-9082-z

Cramer, G. (2024, April 12). *The Art of Investigational Site Relationships with Sponsors/CROs*. ACRP. https://acrpnet.org/2024/04/12/the-art-of-investigational-site-relationships-with-sponsors-cros

Dartmouth Atlas DATA. (2024). *Https://data.dartmouthatlas.org/*. Dartmouth Atlas DATA. https://data.dartmouthatlas.org/

DeSantis, C. E., Miller, K. D., Goding Sauer, A., Jemal, A., & Siegel, R. L. (2019). Cancer statistics for African Americans, 2019. *CA: A Cancer Journal for Clinicians*, *69*(3), 211–233. https://doi.org/10.3322/caac.21555

Dombernowsky, T., Haedersdal, M., Lassen, U., & Thomsen, S. F. (2019). Criteria for site selection in industry-sponsored clinical trials: A survey among decision-makers in biopharmaceutical companies and clinical research organizations. *Trials*, *20*(1), 708. https://doi.org/10.1186/s13063-019-3790-9

FDA, C. for D. E. and. (2023, July 18). *Development & Approval Process | Drugs*. FDA; FDA. https://www.fda.gov/drugs/development-approval-process-drugs

Grabowski, H., DiMasi, J. A., & Long, G. (2024). Postapproval Innovation For Oncology Drugs And The Inflation Reduction Act: Article examines postapproval innovation for oncology drugs and the Inflation Reduction Act. *Health Affairs*, *43*(10), 1400–1409. https://doi.org/10.1377/hlthaff.2024.00202

Jaffe, A. B., Trajtenberg, M., & Henderson, R. (1993). Geographic Localization of Knowledge Spillovers as Evidenced by Patent Citations. *The Quarterly Journal of Economics*, *108*(3), 577–598. https://doi.org/10.2307/2118401

Kilaru, A., Wiebe, D., Karp, D., Love, J., Kallan, M., & Carr, B. (2015). Do Hospital Service Areas and Hospital Referral Regions Define Discrete Health Care Populations? *Medical Care*, *53*. https://doi.org/10.1097/MLR.0000000000000356

Kouvelis, P., Milner, J., & Tian, Z. (2017). Clinical Trials for New Drug Development: Optimal Investment and Application. *Manufacturing & Service Operations Management*. https://doi.org/10.1287/msom.2017.0616

McKibbin, R. (2023). The effect of RCTs on drug demand: Evidence from off-label cancer drugs. *Journal of Health Economics*, *90*, 102779. https://doi.org/10.1016/j.jhealeco.2023.102779

Medicare Part D Prescribers—By Provider and Drug | CMS Data. (n.d.). Retrieved October 29, 2024, from https://data.cms.gov/provider-summary-by-type-of-service/medicare-part-d-prescribers/medicare-part-d-prescribers-by-provider-and-drug

Meinhofer, A. (2018). Prescription Drug Monitoring Programs: The Role of Asymmetric Information on Drug Availability and Abuse. *American Journal of Health Economics*, *4*(4), 504–526. https://doi.org/10.1162/ajhe_a_00101

Méndez, R., Balanzá-Martínez, V., Luperdi, S. C., Estrada, I., Latorre, A., González-Jiménez, P., Feced, L., Bouzas, L., Yépez, K., Ferrando, A., Hervás, D., Zaldívar, E., Reyes, S., Berk, M., & Menéndez, R. (2021). Short-term neuropsychiatric outcomes and quality of life in COVID-19 survivors. *Journal of Internal Medicine*, *290*(3), 621–631. https://doi.org/10.1111/joim.13262

Murata, Y., Nakajima, R., Okamoto, R., & Tamura, R. (2014). Localized Knowledge Spillovers and Patent Citations: A Distance-Based Approach. *The Review of Economics and Statistics*, *96*(5), 967–985.

Olson, M. K., & Yin, N. (2021). New Clinical Information and Physician Prescribing: How Do Pediatric Labeling Changes Affect Prescribing to Children? *Health Economics*, *30*(1), 144–164.

Oshikoya, K. A., Oreagba, I., & Adeyemi, O. (2011). Sources of drug information and their influence on the prescribing behaviour of doctors in a teaching hospital in Ibadan, Nigeria. *Pan African Medical Journal*, *9*(1), Article 1. https://doi.org/10.4314/pamj.v9i1.71188

Ouimet, C., Bouche, G., & Kimmelman, J. (2022). Diminishing clinical impact for post-approval cancer clinical trials: A retrospective cohort study. *PLOS ONE*, *17*(9), e0274115. https://doi.org/10.1371/journal.pone.0274115

Post, B., Norton, E. C., Hollenbeck, B. K., & Ryan, A. M. (2022). Hospital-physician integration and risk-coding intensity. *Health Economics*, *31*(7), 1423–1437. https://doi.org/10.1002/hec.4516

Rambachan, A., & Roth, J. (2023). A More Credible Approach to Parallel Trends. *Review of Economic Studies*, *90*(5), 2555–2591. https://doi.org/10.1093/restud/rdad018

Roberts, T. G., Goulart, B. H., Squitieri, L., Stallings, S. C., Halpern, E. F., Chabner, B. A., Gazelle, G. S., Finkelstein, S. N., & Clark, J. W. (2004). Trends in the risks and benefits to patients with cancer participating in phase 1 clinical trials. *JAMA*, *292*(17), 2130–2140. https://doi.org/10.1001/jama.292.17.2130

Scott, K. W., Orav, E. J., Cutler, D. M., & Jha, A. K. (2017). Changes in Hospital-Physician Affiliations in U.S. Hospitals and Their Effect on Quality of Care. *Annals of Internal Medicine*, *166*(1), 1–8. https://doi.org/10.7326/M16-0125

Skydel, J. J., Luxkaranayagam, A. T., Dhruva, S. S., Ross, J. S., & Wallach, J. D. (2019). Analysis of Postapproval Clinical Trials of Therapeutics Approved by the US Food and Drug Administration Without Clinical Postmarketing Requirements or Commitments. *JAMA Network Open*, *2*(5), e193410. https://doi.org/10.1001/jamanetworkopen.2019.3410

Slejko, J. F., Basu, A., & Sullivan, S. D. (2018). Returns to scientific publications for pharmaceutical products in the United States. *Health Economics*, *27*(2), 282–293. https://doi.org/10.1002/hec.3546

Sood, A., Kappe, E., & Stremersch, S. (2014). The commercial contribution of clinical studies for pharmaceutical drugs. *International Journal of Research in Marketing*, *31*(1), 65–77. https://doi.org/10.1016/j.ijresmar.2013.07.007

Tang, Y., Chang, C.-C. H., Lave, J. R., Gellad, W. F., Huskamp, H. A., & Donohue, J. M. (2016). Patient, Physician and Organizational Influences on Variation in Antipsychotic Prescribing Behavior. *The Journal of Mental Health Policy and Economics*, *19*(1), 45–59.

Thompson, P. (2006). Patent Citations and the Geography of Knowledge Spillovers: Evidence from Inventor- and Examiner-Added Citations. *The Review of Economics and Statistics*, *88*(2), 383–388.