Drug Diffusion through Clinical Trial Sites: Evidence from Physician Prescribing of New Cancer Drugs

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Abstract

Clinical trials benefit patients directly by providing novel treatments, but indirect benefits of clinical trials are less explored. This study analyzes the localized impacts of exposure to clinical trials of new drugs on physician prescribing behavior. Utilizing the prescribing patterns of more than 10,000 physicians across 29 new cancer drugs approved between 2014 and 2019, we find that physicians exposing to clinical trials of new cancer drugs increases the likelihood of prescribing these drugs by 0.18 percentage points, representing a 14% increase relative to the average prescribing rate. Notably, the effects are more pronounced for physicians graduating from higher-ranked medical schools, having more experience and practicing in metropolitans. Further, our results suggest that the exposure to clinical trials reduces the physicians' information acquisition cost of new cancer drugs. Specifically, the cost can be reduced by proximities to trial sites and to the first author of pivotal trial and by affiliation with trial sites.

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. are reported 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 the access to novel treatment, are better understood, but indirectly benefits of clinical trials to patients is 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 the 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). Physicians practicing close to the trial sites respond more than the other

[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 because they experience localized knowledge flow 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 and communication technology and physicians are highly trained to access medical information. There is no clear reason to believe distance to trial sites plays a role in physicians prescribing of new drug.

Our empirical analysis is based on physician-Hospital Referral Region (HRR)-drug-year level data from Medicare Part D prescription dataset for the period 2014–2019. Our dataset contains information, such as practice location and prescribing records, over 10,000 oncologists and other physicians prescribing 29 new cancer drugs over our 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. Based on these data, we leverage the variations of clinical trial timing across 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 HRRs.

We further investigate the heterogeneities in our results. We find that pre-FDA approval clinical trials and post-FDA approval clinical trials have similar impacts on physician prescribing behavior. Physicians graduating from a higher-ranked medical school, having more experienced physicians and practicing in metropolitans are more responsive to their exposure to clinical trials of new cancer drugs. These results suggest that physicians are different in their abilities to acquire the knowledge of new drugs.

Finally, we examine several potential mechanisms underlying the observed effects. First, physicians practicing closer to trial sites of a new cancer drug increase their prescribing rates of that drug relative to the physicians practicing further away from the sites. Second, physicians

practicing close to trial sites that hosting the first author of pivotal trial increases their likelihood to prescribe that drug relative to the physicians only practicing close to other trial sites. Third, physicians practicing close to and affiliated with trial sites of a new cancer drug increase their prescribing rates of that drug relative to the physicians practicing close to but do not affiliate with those sites. These results suggests that the geographic proximity to clinical trial sites reduce the information acquisition cost of new cancer drug and hence increase physician prescribing of those drugs. Particularly, the information acquisition costs can be reduced by geographical proximity, proximity to the first author and organizational proximity.

Our study contributes to the literature that examines how physician responds to scientific information. Particularly, there is a strand of studies examines how physician prescribing responds to the published results of clinical trials.[3] Earlier studies employ drug sales to measure physician prescription and examine how it responds to scientific information. They mostly confirm that the publication of clinic 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 trial 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

[3] 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. See (Ching & Ishihara (2010) and the references citing it.

publications from a pivotal clinical trial of new cancer drug as the scientific information. They conduct their analysis at patient-drug episode level and show that patients are more likely to be prescribed of those drugs when their physicians are geographically proximate to the first author of publications.

To the best of our knowledge, this paper is the first to show physician prescribing in response to their exposure to nearby clinical trials. Our work contributes to the 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 different from the public information studied before, such as publication on medical journal and label released by the FDA. We also identify several mechanisms, such as geographical proximity, local presence of first author of pivotal trial and physician-trial site affiliation, to facilitate the spillover of such localized knowledge.

The rest of the paper is organized as follows. Section 2 describes the background of new drug development and data used in our analysis. Section 3 describes our empirical model. Sections 4 and 5 present the empirical results. Section 6 concludes.

2. Background and Data

2.1 Drug Development

There are multiple phases for a clinic trial sponsor bringing a new drug to market.[4]

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

[4] 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.

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.

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 the 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, that is the post-marketing surveillance. These trials aim to gather more information on side effects, risks, benefits, efficacy, and optimal use, or track its safety in general population.

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, which are typically chosen by the principal investigator. 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 physician prescribing behavior of new drug is a factor of 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 be informed about the new drug. In the remaining of this section, we present the data for investigating the impacts of clinical trial exposure on physician prescribing of new cancer drug.

2.2 Data and Summy Statistics

2.2.1 Physician Prescription Data

We collect the information of physician's prescribing behavior on new cancer drugs, using the Medicare Part D Prescribers - by Provider and Drug dataset provided by the Centers for Medicare & Medicaid Services (CMS).[5] The sample of Medicare Part D claims is suitable for our study because of two reasons. First, 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

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

plans.[6] Medicare Part D claims are likely to provide a representative picture of cancer drug usage of older adults aged above 65.

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 HRR as our 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]

2.2.2 Physician Characteristics Data

Since not all physicians prescribe cancer drugs approved from 2014 to 2019, we select the top related specialties that prescribed those drugs. We include physicians specializing in Hematology, Hematology-Oncology, Medical Oncology and Gynecological Oncology. Also, we do not allow physicians working 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 exposure. This

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

[7] We 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.

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).

2.3 New Cancer Drugs and their 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.

For the trials sites of those new cancer drug, we collect it from *ClinicalTrials.gov* that is 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), trail's phases and when it performs its clinical trials. Besides, 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 Physician Compare dataset, which provide quarterly updates on physicians' affiliations with hospitals and other demographic characteristics from 2014 onwards (Beilfuss and Linde, 2021).[11]

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

We merge this data with our 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.

2.4 Summary Statistics

Our 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 our 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). Till now, Alunbrig has 17 clinical trials in total. We exclude 5 trials in our empirical analysis because one of them began with 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 our over 13,000 sample physicians, we identify 28 physicians from 24 HRR regions prescribed the drug "Alunbrig" between 2017 and 2019. Among those 28 physicians, 15 of them from 11 HRRs in which there was at least one active or completed clinical trial conducted for the drug "Alunbrig".

Our 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 to observe our sample physicians to prescribe a new cancer drug. Our 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 are exposed to the clinical trials of the new cancer drug. Table 2 reports that, on average, there is a 58.2% probability to observe our sample physicians has been exposed to a clinical trial of our sample 29 new cancer drugs. Since there are many research sites perform the clinical trials, there is only a 1.9% probability to observe our sample physicians has been exposed to a clinical trial conducted in a site hosting the leading author. Also, there is only 1.6% probability to observe our sample physicians are affiliated with the research sites that conducted the clinical trials.

Our empirical analysis aims to identify the impacts of clinic trial exposure on physician prescription on new cancer drug. As anecdotal evidence, Figure 1 depicts that there is a significant gap of 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 clinic trial exposure on the physician prescription behavior, we exploit the variations in timing of exposure to clinic trials to identify the causal impact of clinic trials on physician prescribing behaviors. The treated physician in our 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 exposed to any clinic 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 clinic 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 a physician prescribing a new drug after exposed to clinical trials.

Our 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. For instance, we include Phase IV trials, which are conducted after the FDA approval. Also, since clinical trials span several years, some of them may start before the FDA approval while the other in a physician's region may start after the FDA approval. For example, a drug approved in 2015 with a trial had 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.

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

In a later section, we perform a robustness check only keeping the exposure to pre-FDA approval clinical trials, where the treatment variable $Trial_{jd}$ only has the variations at HRR-drug level.

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 HRR and drug level.

4. Empirical Results

4.1. Main Results

We present the results of Equation (1) in Table 3. Column (1) of Panel A in Table 3 reports a statistically significant, precisely estimated 0.18 percentage points increase in the probability of prescribing a new cancer drug associated with clinical trials exposure this year of such a drug. This increase corresponds to a 15.9% increase in the average prescription rate for all sample (1.13% in Table 2).

4.2. Robustness Checks

4.2.1 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 2 presents the results of event studies that examine the impact of clinic trials exposure on physician prescribing behaviors. The coefficients for the years leading up to the clinical trials are relatively flat, indicating no significant pre-treatment trends that could confound the post-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 cancer drugs prescriptions relative to physicians who are never exposed to clinical trials during the sample period. Relative to the pretreatment means of 1.3 percentage points, we associate an exposure to clinical trials with an immediate 25% increase in new cancer drugs prescription. After 2 years, the impact of an exposure to clinical trials on new cancer drugs prescription reached a peak and then return to its original level.

Moreover, there is one limitation for the pre-trend test that even if we can't reject zero pre-trend assumption, we also can't reject pre-trends that under linear or smooth extrapolations to the post-treatment period would produce substantial bias. 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, their proposed test consists of (a) constructing a set Δ of possible deviations from the parallel trends assumption, and (b) constructing the confidence intervals associated with these deviations. We adopt their main robustness tests to extrapolate the estimated linear trend to post-intervention periods and show that our results in event study are robust even when allowing for

significant deviations from the linear extrapolation (see Appendix A.1 for details).

4.2.2 Matching

We use nearest-neighbor propensity score matching to match each of the clinical trials exposure for specific drug that occurred between 2014 and 2019 to a control HRR region. We estimate a separate probit model on a panel sample of drug * physicians from treated HRR regions and the control HRR regions based on drug, year and physician's chracteristics. The probit regressions relate the exposure to clinical trials in the year of treatment to physicians' prescription decision. Using the estimated predicted values as the treatment propensity, we match each treated drug * physician to the untreated drug * physician with the closest propensity score, 81.77% of treated physicians are matched with physicians from control group. However, if treatment HRR regions are characterized by a very different healthcare environment, one concern is that the control units may not represent an adequate counterfactual. To address this concern, we include several healthcare variables from the Dartmouth Atlas Project website (Dartmouth Atlas DATA, 2024) in the matching algorithm and evaluate whether our results are sensitive to the set of variables we add. These variables are: total annual reimbursements per Medicare enrollee (parts A&B), percent of deaths among Medicare enrollees adjusted for age, sex, and race, and average annual percent of diabetic Medicare enrollees age 65-75 who receive hemoglobin A1c test. Table 3 Panel C columns (1) and (2) compared the baseline estimated from Equation (1), estimation with matching algorithm, and with matching algorithm using more healthcare variables, respectively.

4.2.3 Alternative Samples

There is a concern that there are unobserved confounders at HRR level that drives physician prescribing behavior of new drug. For instance, some HRRs have been repeatedly used for clinical trials. In those HRRs, physicians are well-connected to each other and share the news of new drug,

and hence more likely to prescribe new drugs. To handle this confounding situation, we exclude the 5% HRRs with the most clinical trials. Column 2 of Panel A in Table 3 find that the clinical trials exposure still significantly increases the prescription rate of new drugs.

4.2.4 Permutation Tests

We perform a placebo test by randomly assigning clinical trials exposure to physicians to account for any potential over-rejection problem caused by serial correlation. 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 mis-specification of the DD estimation. To increase the identification power of this placebo test, it is repeated 500 times. We report the distribution of these estimates in the placebo tests along with the benchmark estimate, from Panel A column (1) in Table 3. The benchmark estimate is located outside the entire distribution of the placebo estimates, confirming that the results are not likely driven by an over-rejection problem (see Appendix A.3 for details).

4.2.5 HRR with Only One Clinical Trial

As discussed in Section 3, our baseline specification includes HRRs that exposed to multiple clinical trials during the period of study. One may be concerned that physicians from HRRs that are treated multiple times may be somewhat different from the average treated unit and may be disproportionately driving our main findings. To address this concern, we estimate Equation (1) on the subset of HRRs that experienced only one clinical trial for one drug. We conclude that our results are robust to excluding HRRs that are treated multiple times.

4.3 Heterogeneities

4.3.1 Trial Phase Heterogeneity

We estimate Equations (1) for the subsample of clinic trials at different phases and report the

results in Columns 3-4 of Panel A in Table 3. Pre-FDA approval exposure provides physician knowledge about the drug's safety and efficacy in a targeted patient population. Given the drug is already approved by FDA, those Phase IV trials are likely to add information, such as efficacy and side effect, about the drug use for a broader patient population, which is helpful for physician prescribing.

Column 3 reports that the effect of pre-FDA approval trial exposure is 0.0017. This result is also estimated with a specification closer to Agha and Molitor (2018), i.e. $Y_{ijdt} = \alpha * Trial_{jd} + X_j * \beta + \eta_i + \eta_{dt} + \epsilon_{ijdt}$. The treatment occurred before the sample period of physician prescription. Further, Column 4 reports that the effect of post-FDA approval trial exposure is 0.0015. These results suggest both types of clinical trials provide information to physicians about the new drugs and encourage them to prescribe them.

4.3.2 Regional Heterogeneity

We employ an alternative definition of geographical units, i.e. core-based statistical areas (CBSAs).[13] CBSAs represent the universe of metropolitan and micropolitan areas in the U.S. to examine possible geographic variations within HRR region (Maeda et al., 2014; Tomas J. Philipson et al., 2010). In particular, there are three types of area can be defined. Metropolitans have population with 1 million or more persons, Micropolitans have population fewer than 1 million persons (small CBSA/Micropolitan) and Rural (area does not belong to the previous two definition). Column 5-6 of Panel A in Table 3 illustrates those effects of exposure to clinical trials mostly comes from Metropolitan regions ($p < 0.01$). In Micropolitan regions and rural regions, physicians insignificantly respond to an exposure to clinical trials. We suggest the insignificance

[13] https://www.census.gov/programs-surveys/metro-micro.html

results in micropolitan and rural regions relate to their longer distance between physicians and trial sites that weaken the information acquisition (see the next section for further evidence).

4.3.3 Physician Heterogeneity

Panel B of Table 3 show the impact of clinic trial exposure on physician prescribing behavior by physician characteristics. To do so, we divide according to their education in terms of the ranking of their medical school, experience and gender. These characteristics are shown to determine the physician prescribing behavior. Specifically, physicians graduating from top medical schools, older physicians and female physicians are slower to adopt new prescription drugs (Méndez et al., 2021).

Our results in Columns 1-2 (3-4) from Table 3 show that physicians graduated from a Top 15 medical school (physicians with more than 10 years' experience) increase their likelihood to prescribe new drug by 0.57 (0.21) percentage points when they are exposed to the clinic trial of that drug. However, physicians graduated from non-Top 15 medical school and physicians with less than 10 years' experience do not change their prescribing behavior of new drug when they are exposed to the clinic trial of that drug. Further, male physicians increase their likelihood of prescribing new drug more than female physician when they are exposed to a clinic trial of that drug (see Columns 5-6).

Overall, clinic trials have heterogeneous impacts on drug diffusion to physicians. Physicians from a higher-ranked medical school, more experienced physicians and male physicians are more likely to adopt the new drug after exposing to the clinic trials. It suggests supply-side factors are important to new drug diffusion.

5. Potential Mechanisms

We explore three potential mechanisms through which physicians learn to adopt new drug and report the results in Panel C of Table 3.

5.1 Geographical Proximity to the Trial Site

New knowledge is shown to diffuse locally (Jaffe et al., 1993). We examine the relationship between new drug prescriptions and the geographic distance between physician and trial site. Specifically, we generate an indicator for physicians working 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 sub-samples of physician exposing to clinic trials in their counties (Column 1) and the sub-samples of physician exposing to clinic trials in their HRR but not their county (Column 2).

Our results report that physicians exposing clinical trials in their county significantly increases new cancer drug prescriptions by 0.35 percentage points. However, physicians exposing clinical trials in their HRR but not their county significantly increases new cancer drug prescriptions by 0.15 percentage points. These results suggest that the geographic proximity to trial sites reduces the information acquisition cost for physicians to learn about the new drug. These results are also consistent with literature that there is localized knowledge in adopting new technology.

5.2 Geographical Proximity to the Leading Researcher

A factor influencing physician prescribing behavior is 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 researchers can shape their perceptions and decisions.

Column 3-4 examines the impact of an exposure to clinical trials in first-author HRRs compared to an exposure to clinical trials in non-first-author HRRs on physician prescribing behavior. Physicians exposed to clinical trials in first-author HRRs of a new cancer drug demonstrate a statistically significant increase of 0.32 percentage points in the probability of prescribing that drug. This effect represents a substantial 24% rise relative to the average prescribing rate of 1.34% observed in non-first-author HRRs. These findings suggest that the geographical proximity to the trial sites hosting leading researcher disproportionally reduces the information acquisition cost for physicians to learn about the new drug.

5.3 Physician Affiliation with the Research Site

Affiliation between hospitals and physician facilitates the information sharing of hospitals with their affiliated physicians (Post et al., 2022). Affiliation with trial sites may influence 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 5-6 find that physicians increase their prescription rate by 0.34 percentage points when exposed to clinical trials in their affiliated trial site, compared to the 0.17 percentage points observed among non-affiliated physicians. These findings suggest that the affiliation with trial site reduces the information acquisition cost for physicians to learn about the new drug.

6. Conclusion

This study examines the effects of exposure to clinical trials on physician prescribing decision. We find that when a physician is exposed to a 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 across the sample. Moreover, the exposure to clinical trials has a stronger effect on the likelihood of prescribing new cancer drugs for physicians graduating from a higher-ranked medical school and having more experienced, and male physicians. We find that the proximity to trial site reduces information acquisition cost about the new drugs is a potential mechanism driving our results. The reduction of information acquisition cost can derive from three channels: 1) a geographical proximity to the trial site; 2) a geographical proximity to the leading researcher; and 3) an affiliation with the trial site.

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.

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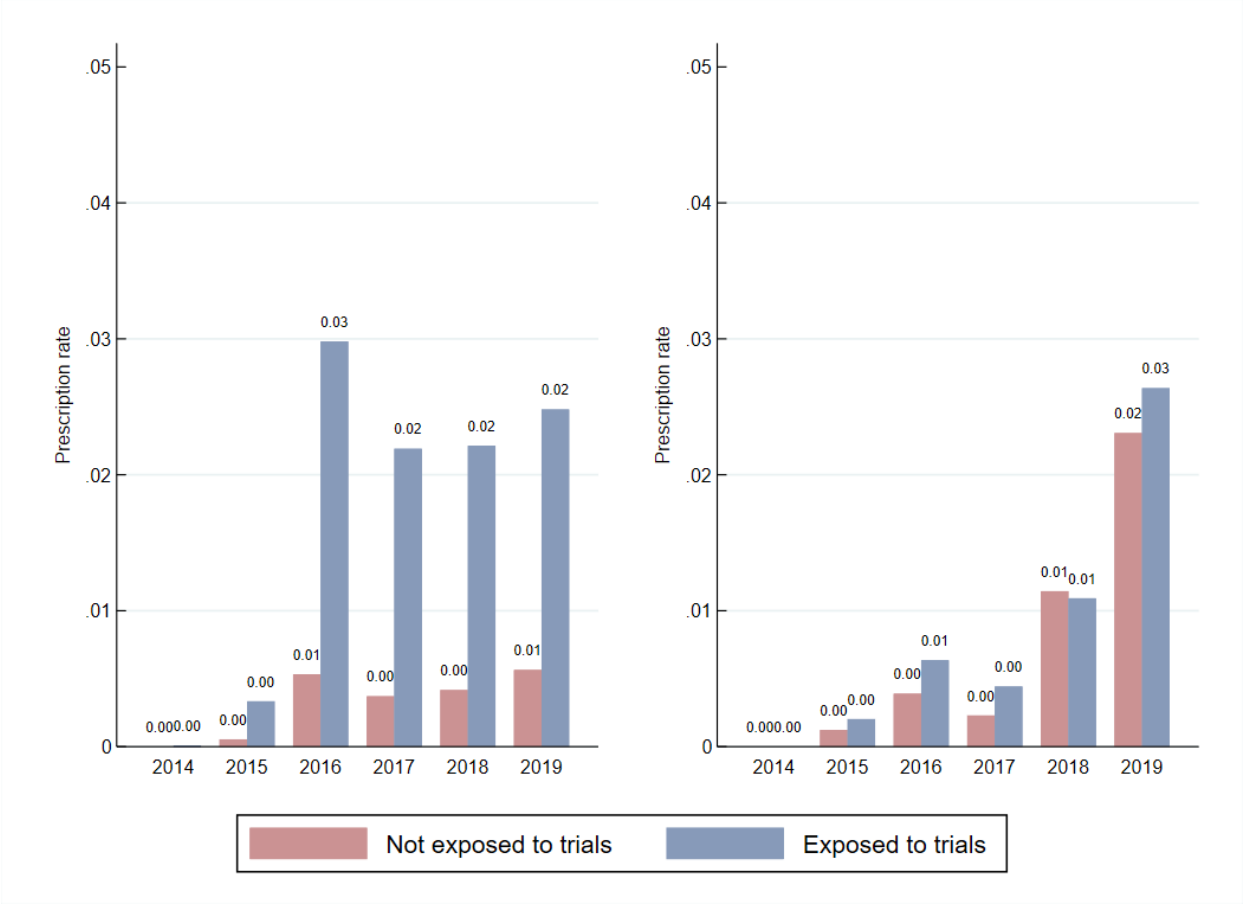

Figure 1. Prescription Rate of Cancer Drugs Over Time

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

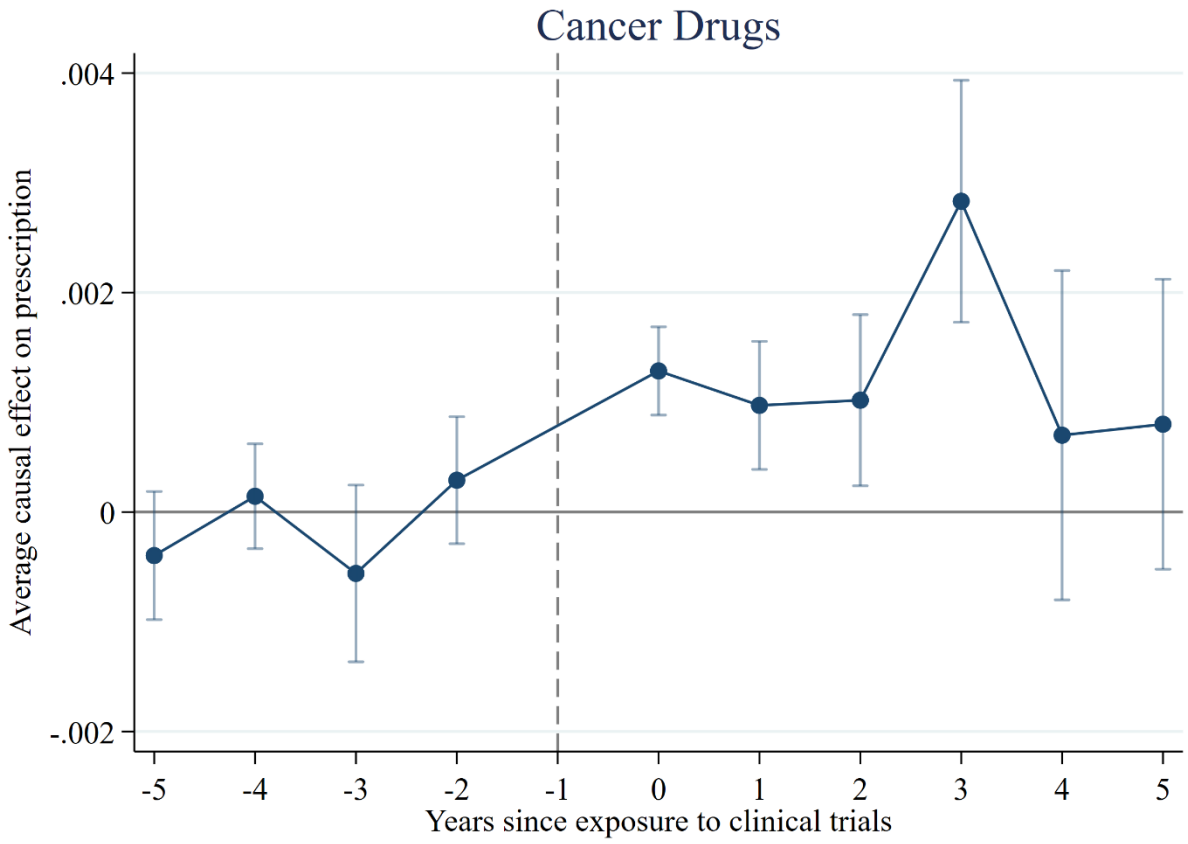

Figure 2. Event Study

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). All specifications include drug-year and physicians FEs. The shaded area in each figure is the 95% confidence interval based on robust standard errors clustered by physicians and drugs level.

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, fallopian tube or primary peritoneal cancers		733	2019		Foreign
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

Note: There were two pivotal trials for Alecensa; the second trial had 19 authors, with the first author in Boston. There were two pivotal trials for Tecentriq; the second trial had 25 authors, 194 sites, with the first author in Germery. We only list the first pivotal trial in the table. Also, in our dataset, we identify one drug "Akynzeo", which was approved twice – initial approval in 2014 and second approval in 2019. We exclude that drug in our sample.

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 our 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 our sample clinical trials because some trials do not list their phases.

Table 3. Effects of Clinical Trials on New Cancer Drugs Prescribing

	(1)	(2)	(3)	(4)	(5)	(6)
Panel A	Clinical Trials		Trial		CBSA Area	
Benchmark & Heterogeneities	Benchmark	Excl.Top 5%	Phase I/ II/III	Phase IV	Metropolitan	Micropolitan/ Rural
Trial	0.0018***	0.0011***	0.0017***	0.0012	0.0019***	-0.0012
	(0.0003)	(0.0003)	(0.0004)	(0.0007)	(0.0003)	(0.0013)
Observations	1,373,216	1,275,768	1,373,216	1,373,216	1,280,656	68,016
Panel B	Sch Ranking		Experience		Gender	
Heterogeneities	Top 15	> 15	<10	≥10	Male	Female
Trial	0.0057***	0.0016***	-0.0003	0.0021***	0.0023***	0.0010***
	(0.0016)	(0.0003)	(0.0008)	(0.0005)	(0.0004)	(0.0004)
Observations	41,776	133,1440	57,181	368,306	798,830	574,386
Panel C	Matching	Matching with	One time			
Robustness		more variables	Exposure			
Trial	0.0085***	0.0023***	0.0001			
	(0.0042)	(0.0004)	(0.0006)			
Observations	1,373,216	1,373,216	422,280			
Panel D	Same County with Trial Sites		Co-locate w/ First Author		Affiliate with Trial Sites	
Mechanisms	Yes	No	Yes	No	Yes	No
Trial	0.0016***	-0.0001	0.0049**	0.0017***	0.0034	0.0017***
	(0.0004)	(0.0003)	(0.0013)	(0.0003)	(0.0018)	(0.0028)
Observations	1,373,216	1,373,216	1,373,216	1,373,216	1,373,216	1,373,216
Physician FEs	Yes	Yes	Yes	Yes	Yes	Yes
Drug-year FEs	Yes	Yes	Yes	Yes	Yes	Yes

Note: Excl. Top 5% = Excluding top 5% HRRs with highest number of clinical trials. Top 15 = Physicians graduated from top 15 medical school.

Appendix A

A.1. Addressing Potential Violations of Parallel Trends

We adopt "relative magnitudes" restriction the main robustness test of Rambachan & Roth (2023), which allows the violation of parallel trends to be no more than M times larger than the worst/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 A1. We see 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.

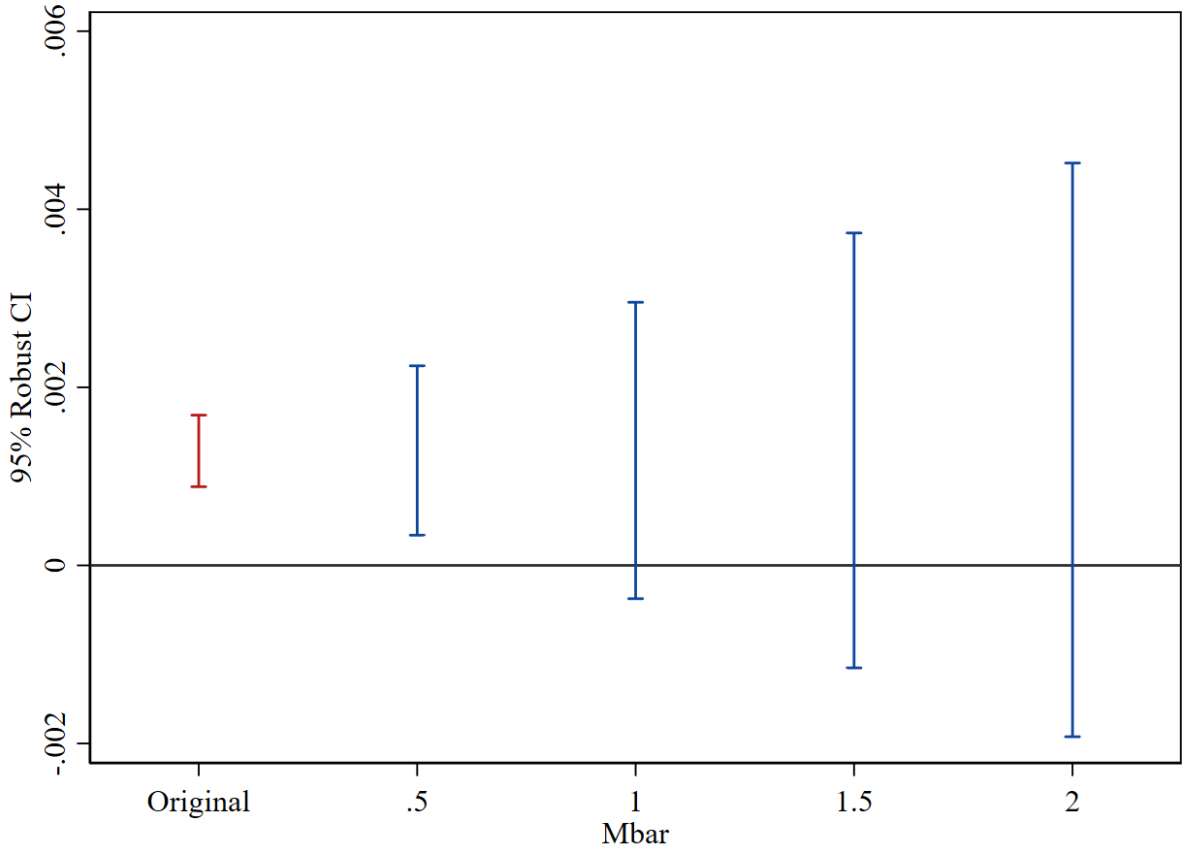

Figure A1. Sensitivity Analysis on Average Effects using Assumptions on the Relative Magnitude

A.2. Alternative Sample

Figure A2 depicts that generally one HRR includes multiple CBSAs and non-CBSAs. CBSAs are useful to examine the heterogeneity within a HRR.

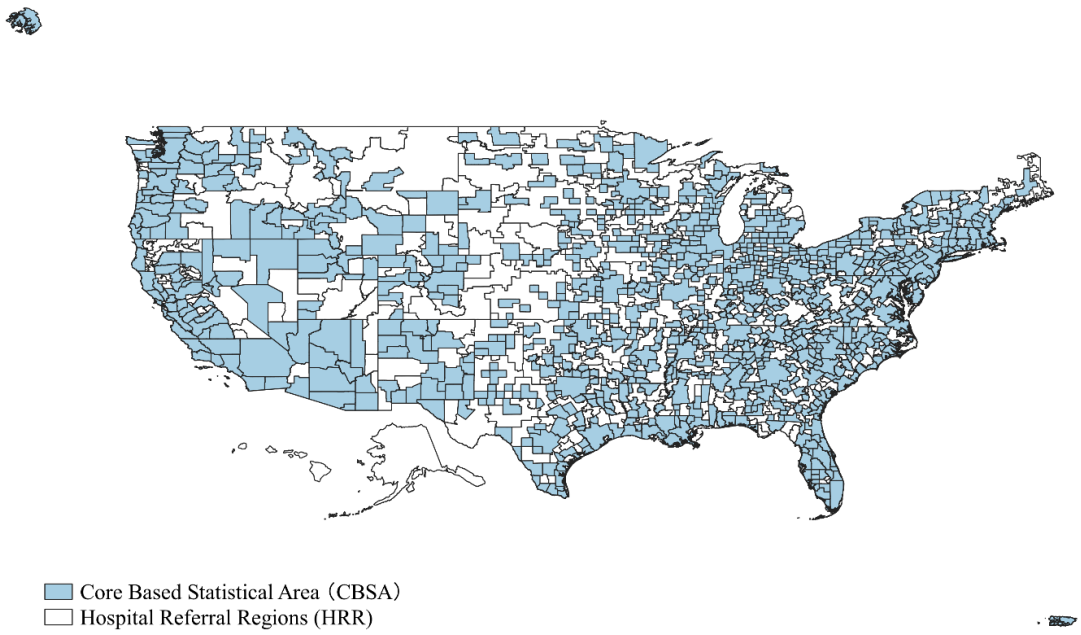

Figure A2. Boundaries of Hospital Referral Regions (HRRs) and Core Based Statistical Areas (CBSAs)

Data sources: U.S. Census Bureau, https://www.census.gov/geographies/mapping-files/time-series/geo/carto-boundary-file.html for CBSA. Dartmouth Atlas of Health Care, https://data.dartmouthatlas.org/#boundaries for HRR.

A.3. Permutation Test

We randomly assign exposure to clinical trials to physicians and estimate our DiD model. We 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.

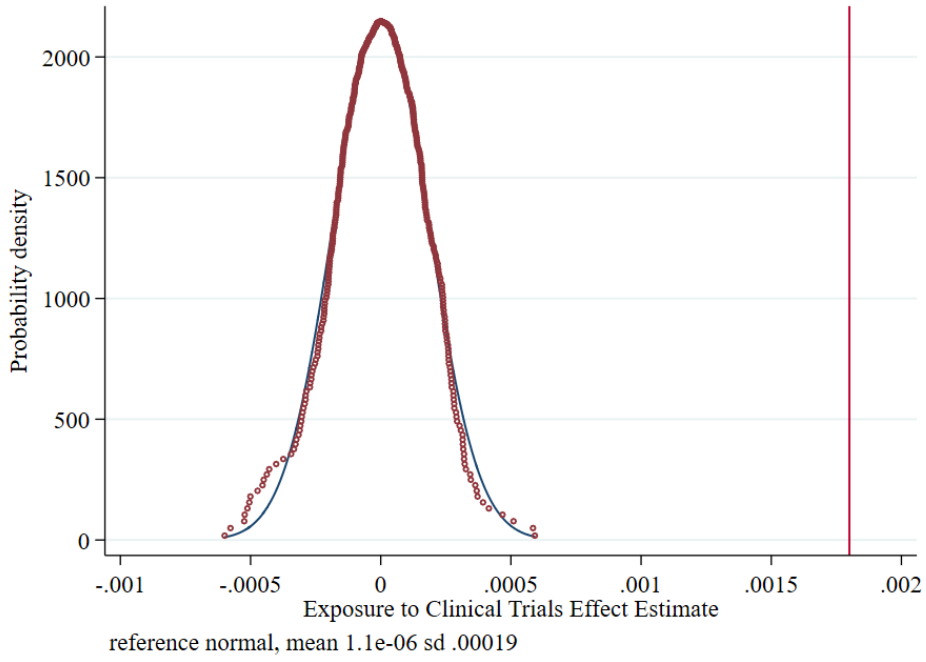

Figure A3. Placebo Test Results

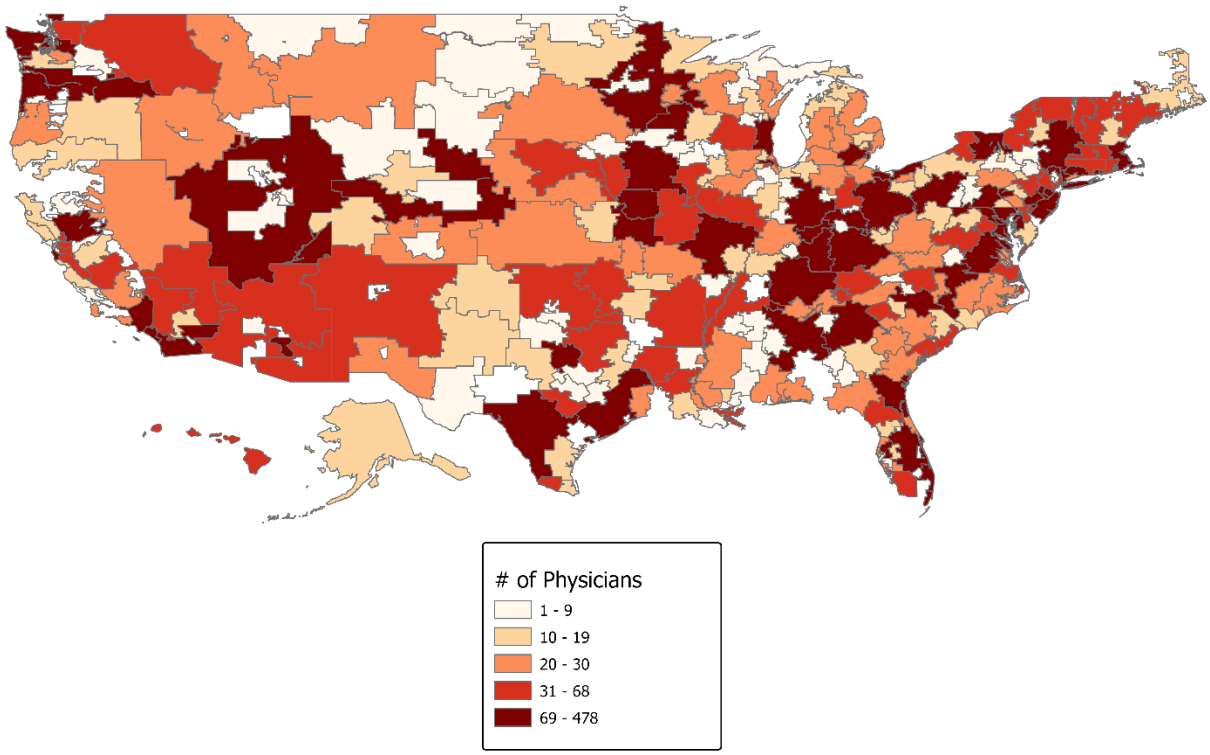

Figure A4. Spatial Variation in Number of Physicians exposed to clinical trials

Notes: This figure displays a map reporting the counts of physicians exposed to clinical trials for each of HRR regions between 2014 and 2019.