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Promoting Innovation in Small Markets: Evidence from the market for rare and intractable diseases

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Promoting Innovation in Small Markets: Evidence from the market for rare and intractable diseases*

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Abstract

In many medical care markets with limited profit potential, firms often have little incentive to innovate. These include the markets for rare diseases, "neglected" tropical diseases, and personalized medicine. Governments and not-for-profit organizations attempt to promote innovation in such markets, but empirical evidence on the policy effect is limited. We study this issue by analyzing the impact of a demand-side policy in Japan, which reduces the cost sharing of patients with some rare and intractable diseases and attempts to establish and promote the treatment of those diseases. Using clinical trials data taken from public registries, we identify the effect of the policy using a difference-in-difference approach. We exploit the institutional detail that the diseases covered by the policy increased in an arbitrary fashion over time. We find that the demand-side policy increased firms' incentive to innovate: firm-sponsored new clinical trials increased by as much as 181% when covered by the policy. This result indicates that the demand-side policy can be an important part of innovation policies in markets with limited profit potential.

Keywords: Rare and intractable diseases, Innovation policy, Demand-side and supply-side policies, Push and pull policies, Clinical trial, Patient cost sharing
JEL Classification: I11, O31, O38

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1. Introduction

Innovation is less likely to occur when the corresponding economic return is expected to be small. This is an important policy issue in many medical care areas where, because of the limited market potential, firms have little incentive to develop treatment procedures. These include the market for rare diseases that have a small number of patients, "neglected" tropical diseases such as dengue fever and rabies that prevail in developing countries, and personalized medicine that tailors treatment to a specific patient group. To encourage innovation in these small markets, various demand-side and supply-side policies that increase revenue and reduce the cost of innovation, respectively, have been proposed and implemented by governments and not-for-profit organizations. A well-known example is the US Orphan Drug Act (ODA) of 1983 that attempted to promote R&D for rare diseases. More recently, to promote drug development for "neglected" tropical diseases, the "priority review voucher" was introduced in the United States in 2007, which grants the developer of a treatment for these diseases an expedited review process that can be transferred to a third party.[1]

Regardless of the importance of the issue, empirical evidence on the effects of policies that aim to promote innovation in small markets is limited. This paper aims to fill this gap by analyzing the impact of a demand-side policy that reduces cost sharing of patients with rare and intractable diseases in Japan. By reducing patient cost sharing, the government aims to establish and promote the treatment of rare and intractable diseases that are extremely difficult to treat and reduce the high medical expenses that patients incur.[2] Thus, one of the main objectives of the policy is to promote innovation using the demand-side instrument. Reducing the cost of medical treatments may encourage patients to seek more medical treatments, and the resulting increase in revenue may encourage firms to engage in more R&D activities on those diseases. If, on the other hand, receiving treatment of intractable diseases is not discretionary to the patient, then reducing cost sharing will affect neither the size of the market nor firm behavior.

We attempt to identify the effect of the government policy on R&D activities using a difference-in-difference (DID) approach. In 2009, as part of an economic stimulus package after the financial crisis in 2008, the Japanese government added 17 intractable diseases to the list of diseases eligible for reduced cost sharing.[3] Our basic idea of

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[1] Please see Ridley et al. (2006) for more about the "priority review voucher."

[2] For the objectives of the policy, see http://www.nanbyou.or.jp/pdf/kousei21_1.pdf (In Japanese. Accessed March 17, 2016.)

[3] According to the government announcement, 11 diseases were added to this list. However, the government also subdivided one disease category, diencephalo-hypophysial dysfunction, into seven

identification is to compare the number of new clinical trials over time for the diseases added to the list in 2009 with those of other similar intractable diseases that were not eligible for reduced cost sharing throughout the data period. To determine the control group, we exploit an institutional detail. Traditionally, the number of diseases eligible for reduced cost sharing has been small and, moreover, the choice of diseases has been criticized as being arbitrary and unfair. In 2015, the government redefined the eligibility for reduced cost sharing and expanded the coverage to more than 300 diseases. This implies that there were many other diseases that deserved the same benefit in 2009 but did not obtain it until 2015. We use the latter diseases as controls.

Our main data are from Japan's primary registries, which are public databases containing information on clinical trials. We carefully searched the databases using a number of keywords and identified clinical trials related to the intractable diseases we study. This original data set covers the period between October 2005 and September 2014 and contains the names of the drugs or devices in trial, trial start date, trial phase, and whether the trial was conducted by a sponsor firm or physician-led. We also collected additional data on the number of patients with the diseases.

Our findings can be summarized as follows. First, we find that reduced cost sharing for rare and intractable diseases increased the number of firm-sponsored clinical trials as much as 182% when covered by the policy. This implies that even for intractable diseases for which patients seem to have little discretion to receive treatments, reduced cost sharing appears to increase the market size, which in turn encourages firms to increase R&D activities on those diseases. Second, we find that the estimated impact was large relative to the average number of clinical trials per disease before the policy was implemented. Thus, the demand-side policy can be an important part of innovation polices that aim to stimulate R&D on drug and medical devices with limited market potential. Third, the observed results were found in phase II, and not in phase I. One interpretation of this result is that the primary effect of the policy is to encourage firms to conduct additional trials for existing drugs and devices but not necessarily to initiate an entire new line of product development.

To our knowledge, few studies have examined the effects of innovation policy on markets with small profit potential. One notable exception is Yin (2008) who studied the impacts of the ODA in the United States. The ODA intended to increase pharmaceutical innovations for rare diseases that affected less than 200,000 patients by extending market exclusivity periods (demand-side policy) and by reducing R&D costs through

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specific diseases and specified their names in the list. This makes the number of added diseases 17. We use the finer disease categories in this paper.

tax credits (supply-side policy). Yin found that by comparing with the diseases that affected just above 200,000 patients, the ODA increased the number of clinical trials for rare diseases that affected less than that number. Our study differs from his in three ways. First, the type of demand-side policy we examine (reduced cost sharing) differs from that used in the ODA (market exclusivity). Moreover, while we focus on the impact of the demand-side policy, Yin's estimate captures the combined effect of the demand-side and supply-side policies that constitute the ODA. Thus, Yin's evidence may not be informative for policymakers who wish to understand the impact of either of the policies. Second, the Japanese policy targets rare and intractable diseases, while the ODA is only concerned with rarity. The results could be different if, for example, patients with intractable diseases have more inelastic demand for medical treatments. To our knowledge, no previous study has examined whether R&D activities for intractable diseases respond to government policies.

The studies by Finkelstein (2004) and Blume-Kohout and Sood (2013) are also closely related to ours. Finkelstein (2004) found that health policies that promote the utilization of existing vaccines, such as the 1991 CDC recommendation that all infants be vaccinated against Hepatitis B, also affects incentives to develop new vaccines. Blume-Kohout and Sood (2013) found that the introduction of Medicare Part D in the United States is associated with increases in pharmaceutical R&D for drug classes with higher Medicare market share. A notable difference between ours and their studies is that, while we focus on examining the effectiveness of a demand-side innovation policy, the above studies highlight that health policies that affect demand may also unintendedly affect R&D.[4]

Our study also relates to the studies that examined the relationship between market size and innovation using data from the pharmaceutical markets (i.e., Acemoglu and Linn, 2004; Dubois et al. 2015). Again, our paper differs from these studies because, while the main focus of these studies is to carefully identify the impact of market size on innovation, our focus is to evaluate the impact of a demand-side innovation policy on R&D activities.

Our study also contributes to the literature on the impact of innovation policy. Traditionally, the focus of innovation research has been on the supply side and very few studies have explicitly looked at the demand side. In particular, a large literature exists on the effect of tax credits on R&D expenditure, which consistently found a positive

[4] Kyle and McGahan (2012) also examined whether the passage of the TRIPS Agreement, which increased the levels of patent protection, increased R&D activities, finding that such effects were present in developed countries but not in developing countries.

relationship between the two (please see Hall and Van Reenen, 2000, for a survey). Our study complements this literature by providing new evidence on the effect of a demand-side instrument on R&D.

The remaining sections are organized as follows. In Section 2, we briefly describe the policies toward rare and intractable diseases in Japan. Section 3 describes the data we use in our analysis. In Section 4, we discuss identification issues and our empirical model. Section 5 reports the estimation results. In Section 6, we discuss our findings in reference to previous studies. We conclude our study in Section 7.

2. Background

Since 1972, the Japanese government has introduced demand-side and supply-side policies that aim to develop treatment procedures for rare and intractable diseases.[5] One notable feature of the policies is that they target diseases that are not only rare but also intractable. This is in contrast to the ODA in the United States, where the primary focus is rarity, not intractability.

The supply-side policy. The government provides grants for research projects that aim to identify the causes and develop treatment procedures for the diseases that satisfy the following conditions: the disease is rare, the cause is unknown, no established treatment exists, and it has a high risk of long-term disability. As of 2009, 130 diseases were eligible for the research grant.[6] These diseases were chosen based on the recommendation of a government advisory board. Each year, the government allocates a research budget specifically for these diseases and gives grants on a competitive basis.

The demand-side policy. In 1973, the government started implementing a policy that reduces patient cost sharing for a subset of intractable diseases targeted by the supply-side policy.[7] This demand-side policy is the main focus of this paper. Japan implements universal health coverage, and patients below age 70 pay coinsurance of 30% for any medical treatment covered by public health insurance.[8] Because intractable diseases cannot be completely cured, medical spending for the patient can be quite high and be required for a long period. The demand-side policy reduces patients' out-of-pocket spending by setting a stop-loss, a maximum amount of monthly out-of-pocket expenditure, for the treatment of qualified intractable diseases, which ranges between 0 to 23,100 yen per month based on their family income. The stop-loss

[5] For more details about Japanese policies for intractable diseases, please see http://www.nanbyou.or.jp/entry/4141 (in Japanese. Accessed January 20, 2016).
[6] The Japanese name of the program is *Nanchisei sikkan kokuhuku kenkyu jigyo*.
[7] *Tokutei sikkan chiryo kenkyu jigyo* in Japanese.
[8] The coinsurance for the elderly above age 70 was 10% during our data period.

for the patient with a qualified disease is substantially lower than that for other diseases: for all other diseases, patients have to pay up to 80,100 yen per month before the stop-loss applies. In 2010, 706,720 patients were registered with qualified diseases[9] and the total amount of subsidy was 109 billion yen.[10]

The government reduces patient cost sharing, in part because for these diseases, identifying the causes and developing treatment procedures were deemed difficult without the government's financial support for the patient. Thus, an intention of the policy was to promote R&D through reduced cost sharing. To qualify for reduced cost sharing, certain diagnostic criterion had to exist for the disease, in addition to the four conditions required for the supply-side policy. The number of intractable diseases that qualify for reduced cost sharing has been small. As of 2005, only as few as 45 out of 5000 to 7000 intractable diseases were eligible for reduced cost sharing. Moreover, as we discuss in detail in Section 3, the diseases covered by the policy have been chosen in a rather arbitrary way. We exploit this institutional detail to identify the effect of the policy.

The Orphan drug/medical device designation. The government also has an ODA-type policy that promotes R&D of orphan drugs/medical devices. Drugs and medical devices that satisfy the following conditions are designated as orphan: (1) less than 50,000 patients in Japan, (2) identified as serious diseases with high medical needs, and (3) a high probability of development. Designated orphan drugs and medical devices can receive government support including tax credit on research expenses, extended market exclusivity of 10 years, and a priority review.[11] Similar to the US policy, the Japanese orphan policy targets rare diseases and is not particularly concerned with intractability.

The orphan drug/medical device policy was implemented in 1993 and was in place throughout our data period (i.e., 2005-2014). Moreover, unlike the demand-side policy toward intractable diseases, it does not apply to specific diseases. Thus, although it is closely related to the policies toward intractable diseases, the orphan drug/medical device policy does not directly affect our study, which exploits the fact that the diseases that were qualified for reduced cost sharing changed over time.

[9] Source: http://www.nanbyou.or.jp/entry/1356 (in Japanese. Accessed February 18, 2016).
[10] Source: http://www.mhlw.go.jp/stf/shingi/2r9852000002ucax-att/2r9852000002ucez.pdf (in Japanese. Accessed February 18, 2016).
[11] For more details, please see http://www.mhlw.go.jp/english/policy/health-medical/pharmaceuticals/orphan_drug.html (Accessed January 9, 2016).

3. Identification and empirical models

We attempt to identify the effects of reduced patient cost sharing on the number of clinical trials using the DID approach. Prior to 2009, patients with 45 intractable diseases out of 130 diseases that were eligible for research grant enjoyed reduced cost sharing. In October 2009, the Japanese government added 17 intractable diseases to this list as part of an economic stimulus package after the financial crisis in 2008. Even after this expansion, only 62 intractable diseases received reduced cost sharing and the choice of eligibility has been criticized as arbitrary and unfair.[12] Responding to these criticisms, in 2015, the government reevaluated the conditions for reduced cost sharing and expanded the coverage to more than 300 diseases.[13] These developments imply that, in 2009, there were many other diseases that deserved the same benefit of reduced cost sharing but did not receive it because of the arbitrariness of the selection of eligible diseases.

We exploit this institutional detail to construct the treatment and control groups. The treatment group consists of diseases that became eligible for reduced cost sharing in 2009 and continue to be eligible in 2015. The control group consists of diseases that were not eligible for reduced cost sharing in 2009 but became eligible in 2015. To further control for the effects of the supply-side policy, we further restrict our attention to the diseases that were included in the 130 diseases that were eligible for research grant in 2009. As a result, we have a total of 46 intractable diseases in our study. The treatment group consists of 15 diseases that became eligible for reduced cost sharing in 2009.[14] The control group consists of the remaining 31 diseases.

At least three potential concerns for the identification strategy should be discussed. First, if industry participants anticipated the policy change, the DID approach may not accurately capture the impact of the policy change. This concern is probably not serious because the financial crisis in 2008 triggered the addition of the 17 diseases; thus, it is unlikely to have been anticipated by the industry. The second concern is reverse causality: unlike our theory that reduced cost sharing increases R&D activities, diseases with a more promising line of treatment might have been chosen for reduced cost sharing from among alternative diseases. However, according to the conference minutes of the meeting that advised the inclusion of the diseases to the government, the diseases

[12] Please see a remark by a government official at http://www.mhlw.go.jp/stf/shingi/0000054843.html (Accessed January 24, 2016).

[13] For example, a disease is now defined to be “rare” when the number of patients is less than 0.1% of the population.

[14] The treatment group consists of 15 diseases, rather than 17, because one was excluded from the list of diseases eligible for reduced cost sharing in 2015 and another was not among the 130 diseases that were eligible for research grant in 2009.

of "highest vital importance" for patients were chosen from among the requests by patient groups.[15] Thus, it is unlikely that the diseases that had treatment procedures and were ready for clinical trials were chosen for reduced cost sharing. Third, it may be the case that the allocation of research grant (i.e., the supply-side policy) is influenced by whether the disease is eligible for reduced cost sharing. If true, even if reduced cost sharing increases R&D activities, the observed impact does not reflect the mechanism of our interest, that is, reduced cost sharing increases the profitability of the market, which in turn increases R&D activities. However, we believe that this concern is not serious because grants are given based on the scientific merit of the research, not on whether the disease is eligible for reduced cost sharing.

In our empirical implementation, we estimate the following four models. Our base is a simple linear DID model:

$$N_{jt} = \boldsymbol{A}_t + \boldsymbol{B}_j + \alpha_1 POST_{jt} + \boldsymbol{X_{jt}}\beta_1 + \varepsilon_{jt} \quad (1)$$

where N_{jt} is the number of new clinical trials for disease j in year t. $\boldsymbol{A_t}$ and $\boldsymbol{B_j}$ are year and disease fixed effects, respectively. We construct the data so that year t starts in October of each year. This reflects the fact that the 2009 policy change took place in October.[16]

$POST_{jt}$ is the dummy variable of our interest, which equals 1 if disease j is eligible for reduced cost sharing in year t and 0 otherwise. $\boldsymbol{X_{jt}}$ is a vector of control variables. In this specification, we include a dummy variable that equals 1 if disease j was eligible for a research grant in year t.[17] ε_{jt} is an error term. In all four models that we estimate, standard errors are corrected for clustering at the disease level, which allows the error terms to be correlated over time within each disease.

As shown in Figure 1, our second model recognizes that the impact of reduced cost sharing on R&D activities gradually increased over time. To capture this pattern in the data, we replace POST in equation (1) by POSTTREND, an interaction term between POST and the number of years after the policy change.[18] Specifically, we estimate the

[15] The conference minutes are available at http://www.mhlw.go.jp/shingi/2009/09/txt/s0917-7.txt (Accessed January 7, 2016).

[16] We also experimented with different data periods such as quarterly or semi-annually. Unfortunately, estimating the model became difficult as we disaggregate the data. This is perhaps because we observe a relatively small number of clinical trials for intractable diseases.

[17] As we discussed in Section 3, as of 2009, all diseases in our sample were eligible for research grant and thus covered by the supply-side policy. However, two diseases became eligible for research grant between 2005 and 2009. We control for this variation by the research grant dummy variable.

[18] For example, in the first year after policy change POSTTREND = POST*1. Similarly, in the second year, POSTTREND = POST*2.

following model:

$$N_{jt} = \boldsymbol{A}_t + \boldsymbol{B}_j + \alpha_2 POSTTREND_{jt} + \boldsymbol{X_{jt}}\beta_2 + \varepsilon_{jt} \quad (2)$$

where all variables other than POSTTREND are the same as in equation (1).

We also estimate the following "dynamic" model, which is more flexible in terms of the timing that the policy change affects development activities.

$$N_{jt} = \boldsymbol{A}_t + \boldsymbol{B}_j + \sum \alpha_t d_{jt} + \boldsymbol{X_{jt}}\beta + \varepsilon_{jt} \quad (3)$$

where d_{jt} is the dummy variable that equals 1 if it is in year *t* and disease *j* was eligible for reduced cost sharing after 2009, and 0 otherwise. The remaining variables are the same as before. This specification also allows us to check whether there was a pre-existing time trend before the implementation of the new policy in 2009. In particular, we do not expect α_t to be positive until the policy was implemented in 2009.

Finally, as an alternative to the linear models, we also estimate a count data model that recognizes that our dependent variable has integer values. Specifically, we estimate a Poisson model in the following form:

$$N_{jt} = f\left(\boldsymbol{A}_t + \alpha_1 POST_{jt} + \boldsymbol{X_{jt}}\beta + \varepsilon_{jt}\right) \quad (4)$$

where $\boldsymbol{A}_t$ and $POST_{jt}$ are the same as before. In this model, we do not include disease fixed effects because of the incidental parameter problem in non-linear models. Instead, we include two additional variables in $\boldsymbol{X_{jt}}$: disease *j*'s market size in terms of the number of patients[19] and a dummy variable that equals 1 if disease *j* was eligible for reduced cost sharing after October 2009.

4. Data

Our main data are from Japan's primary registries, which are public databases containing information on clinical trials. There are three WHO approved primary registries in Japan, namely, UMIN CTR, JapicCTI, and JMACCT CTR.[20] Registering a clinical trial on a public registry is not mandatory. However, since around 2005, registering a clinical trial on a public database has become a standard practice in the

[19] We only have one number for each disease. Thus, the market size data do not vary by year.

[20] These databases are available online. UMIN CTR: https://upload.umin.ac.jp/cgi-open-bin/ctr/ctr.cgi?function=search&action=input, JapicCTI: http://www.clinicaltrials.jp/user/cteSearch.jsp, JMACCT CTR: https://dbcentre3.jmacct.med.or.jp/JMACTR/App/JMACTRS03/JMACTRS03.aspx?kbn=14 (in Japanese. Accessed January 29, 2016).

medical community. In September 2004, major medical journals, including Lancet and JAMA, made registering on a public registry a prerequisite for publication.[21] In January 2005, pharmaceutical industry organizations worldwide declared that they would register clinical trials on a publicly accessible database.[22] In April 2005, the Ethical Guidelines for Clinical Research released by the Japanese Ministry of Health, Labour and Welfare (MHLW) stated that researchers are encouraged to make their clinical trial plans and results public.[23] Additionally, the Japanese primary registries mentioned above started operations in 2005. Following these developments, we focus on clinical trials that started after April 2005. We use data up to September 2014 because in the next month, the government announced the new policy that expands the coverage to more than 300 diseases, which became effective in 2015.

We extensively searched the registries and identified clinical trials that were related to the intractable diseases of our interest. We carefully constructed keywords by recognizing that each disease can be described in multiple ways and can have different abbreviations. We first consulted with Japan Intractable Diseases Information Center[24] for possible descriptions of each disease. After conducting initial screening with these keywords, we redefined search keywords based on the descriptions that appeared in the identified clinical trials. For example, in the case of the POEMS syndrome, our keywords include Fukase, POEMS, monoclonal, and Takatsuki (a Japanese name of the disease). We checked the descriptions of all clinical trials we searched for so that the trials we found indeed were intended to treat the intractable diseases of our interest. In Appendix A1, we describe in more detail how we constructed the data.

From the registries, we extracted the name of the targeted disease, the name of drug or device in trial, trial start date, trial phase (i.e., phases I, II, and III), and whether the trial was sponsored by a firm or physician-led.[25] In this study, we focus on the clinical trials that aim to receive the manufacture and sales approval of the government.[26] Clinical trials can be grouped into firm-sponsored and physician-led

[21] http://www.icmje.org/news-and-editorials/update_2005.html (Accessed January 24, 2016).
[22] Please see http://www.ifpma.org/fileadmin/content/Ethics/Clinical_Trials/Nov2009_Joint_Position_CT_Data_Disclosure_registries_and_databases.pdf (Accessed January 24, 2016).
[23] http://www.mhlw.go.jp/general/seido/kousei/i-kenkyu/rinri/0504sisin.html (Accessed January 22, 2016).
[24] http://www.nanbyou.or.jp/ (Accessed January 6, 2016).
[25] Phase I trials evaluate the safety of a drug or device in a small group of people. Phase II trials test the efficacy of a drug or device (i.e., whether it works as intended) in a larger group of people. Phase III trials evaluate whether a drug or device is better than a standard or other treatment in an even larger group of people.
[26] For example, physicians may conduct clinical tests for the purpose of publishing a paper in a medical journal. We excluded such tests from our final data set.

trials. Prior to 2003, only firms could conduct clinical trials. However, when the market size is small, firms may not have an incentive to conduct clinical trials even if there is a drug or device that could potentially treat a disease. The physician-led clinical trial was introduced to address this issue. In physician-led trials, physicians typically not only plan and manage the trial, but also raise funds for it.

Table 1 presents summary statistics. The unit of analysis is disease per year. We have a total of 414 (=46 diseases*9 years) observations. The average number of clinical trials is 0.11 per disease per year. Although this number is small, it is comparable to the corresponding figure for the United States, which was 0.07 between 1984 and 1994.[27] The number of patients ranges between 20 and 66,300. Among the three trial phases (phases I, II, and III), phase III trials are more frequently observed in the data, followed by phase II trials. We have very few phase I trials in the data. Comparing trials, 55% are firm-sponsored and the remaining 45% are physician-led. Appendix A2 lists all diseases included in the analysis along with the number of patients and whether the disease is eligible for reduced cost sharing.

Figure 1 shows the cumulative number of clinical trials per disease over our data period. The red and blue lines correspond to the treatment and control groups, respectively. T = 0 indicates the month of October 2009 when additional diseases became eligible for reduced cost sharing. This figure indicates that until October 2009, the trends for number of clinical trials per disease were very similar in both groups. A few years later, however, the trends started to diverge and the number of clinical trials substantially increased for the diseases eligible for reduced cost sharing (i.e., the treatment group). This provides initial evidence that reduced cost sharing positively affected R&D activities. In the next section, we examine this relationship more formally using econometric models.

5. Results

Results for the base model

In Table 2, we report the estimation results from equation (1), that is, our base model. Column 1 shows the results for all clinical trials, while columns 2 and 3 report the results for firm-sponsored and physician-led clinical trials, respectively. Column 1 shows that the coefficient on POST is positive but not statistically significant, indicating

[27] The average number for the United States was calculated from the number of clinical trials reported in Figure 1 of Yin (2008); a total of 795 clinical trials were conducted for 1023 rare diseases during the 11-year period.

that at the aggregate level, there is no evidence that reduced cost sharing increases clinical trials. Columns 2 and 3 show an interesting contrast; column 2 indicates that reduced cost sharing significantly increases firm-sponsored clinical trials, while column 3 suggests that physician-led trials are unaffected. The result for firm-sponsored trials suggests that reduced cost sharing raised the expected profit of developing treatments for those diseases, which in turn increased related R&D activities by firms. The lack of a statistically significant result for physician-led trials may not be surprising, because such trials are typically not funded by firms and the increased profit potential may not motivate physicians to conduct additional trials. The estimated coefficient for firm-sponsored trials in column 2 indicates that reduced cost sharing increased firm-sponsored clinical trials for rare and intractable diseases by 0.16 per disease per year. This implies a 181% increase in the number of clinical trials relative to the average in the year immediately before the implementation of the policy. Thus, the impact of reduced cost sharing on development activities is substantial.

In columns 4 and 5, we report the results that separately examined the impact of reduced cost sharing on the three phases of firm-sponsored clinical trials. The aim of the analysis is to obtain a glimpse of whether reduced cost sharing encourages firms to initiate a new product development, which may be reflected in the increase of phase I or later-phase trials (i.e., phases II and III), on existing drugs and devices that might have been shelved in the absence of the government policy. We find that the impact of reduced cost sharing is statistically significant for phase II trials. In contrast, we could not even estimate the model for phase I trials. One interpretation of the results is that the reduced cost sharing encouraged R&D activities on existing drugs and devices (as opposed to new drugs and devices) on which phase I trials had already been conducted but firms were reluctant to proceed to phase II trials due to limited profit potential.

Results for the linear trend model

Table 3 reports the results from equation (2) which assumes that the impact of reduced cost sharing increases gradually over time. Column 1 reports the results for all clinical trials, in which we do not find evidence that reduced cost sharing increased clinical trials in total. Columns 2 and 3 report the results for firm-sponsored and physician-led clinical trials, respectively. Similar to the results reported in Table 2, we find that reduced cost sharing significantly increased the former but not the latter. Moreover, the result for firm-sponsored trials indicates that the impact of reduced cost sharing increases linearly year by year over time. The estimated parameter value suggests that in the fifth year since the introduction of the policy, clinical trials per disease per year

increased by approximately 0.27. The model also suggests that the impact could be even greater in later years. The growing impact over time is reasonable because it takes time to initiate clinical trials.

Columns 4 and 5 report the results that further separate the firm-sponsored trials by trial phases. These results indicate that the increase in firm-sponsored clinical trials is driven largely by those in phase II. These results are consistent with the results found in columns 4 and 5 of Table 2.

Results for the "dynamic" model

We now turn to the results from the "dynamic" model defined by equation (3). This model allows us to understand when reduced cost sharing affected R&D activities. As noted before, this model also allows us to check whether there was a pre-existing time trend for the diseases eligible for reduced cost sharing. Table 4, Column 1 reports the results for all clinical trials. In Figure 2, we also show graphically how α_t, the coefficient on d_{jt}, changes over time. We use t-2, that is, the period between October 2007 and September 2008, as the baseline for the time trend. First, Figure 2 suggests that reduced cost sharing had little effect on R&D activities before the introduction of the policy. This confirms the finding in Figure 1 that the treatment and control groups followed a similar trend before the former group became eligible in 2009. Second, Figure 2 indicates that the impact of reduced cost sharing was not immediate after October 2009 and instead took more than two full years before it had effects. This result alleviates the reverse causality concern that the diseases that were experiencing important technological progress were chosen for reduced cost sharing and not vice versa.

The results reported in Table 4, column 1 support these discussions. In particular, we find that the coefficient on t+2 (the third year after the policy change) is positive and statistically significant, indicating that reduced cost sharing significantly increased clinical trials but the effect was delayed until t+2. The estimated coefficient indicates that the reduced cost sharing increased the number of clinical trials by 0.22 per disease per year in the third year. This is a large increase relative to the pre-policy average of 0.087.[28]

Results for the count data model

[28] We also run the same regression by firm-sponsored versus physician-led and by phase, but failed to find significant results at the conventional level. After allowing for different effects by year, the data do not appear to have enough variations to identify the effects of reduced cost sharing at a further disaggregated level.

Table 5 reports the estimation results for the Poisson model. Column 1 reports the results for the entire sample, which indicates that at the aggregate level, reduced cost sharing has little effect on clinical trials. Column 2 reports the results for the firm-sponsored clinical trials. The results indicate that, as in the case of the linear models, reduced cost sharing has a positive and significant effect on the number of new clinical trials. The estimated marginal effect suggests that the demand-side policy increases firm-sponsored clinical trials by 0.15 per disease per year. Note that this number is almost the same as the result from the linear model discussed previously. Estimating the count data models was generally more difficult than that of linear models and we were unable to obtain estimates for the physician-led trials. Nonetheless, the results we obtained are very similar to those from the linear models, thus providing additional confidence in our results.

To summarize, three empirical regularities emerged from the econometric analysis. First, reduced cost sharing increased the number of firm-sponsored clinical trials but not the physician-led trials. This result is reasonable because, while firms would be responsive to the change in revenue potential, physicians may not obtain a direct benefit from an increased market size. Second, the immediate impact of reduced cost sharing was small and the impact increased gradually over time. One of our models indicates that the impact could be even greater in later years. Third, among the three phases of clinical trials we examined, the effect of reduced cost sharing was apparent only in phase II trials. The fact that we did not find the same results for phase I trials may imply that reduced cost sharing primarily encouraged clinical trials of existing drugs and devices whose phase I trials had already been performed but, perhaps, because of limited market potential, firms did not proceed to later stage trials.

6. Conclusions

In many medical care markets with limited profit potential, firms often have little incentive to innovative. Promoting innovation in such markets is an important policy issue that is common across countries. Policymakers have considered and implemented various supply-side and demand-side policies that encourage innovation in such markets, but relatively little evidence exists on the effects of such policies.

Focusing on a demand-side policy that lowers patient cost sharing for the treatment of rare and intractable diseases, we examined whether such a policy affects firms' incentive to innovate. If reduced cost sharing increases the revenue potential, the policy would increase the incentive to innovate. If, on the other hand, patients with intractable

diseases have little or no discretion to receive medical treatments, reduced cost sharing would not affect firms' innovative activities.

Using clinical trials data taken from public registries, we identified the effect of the policy using the DID approach, exploiting the institutional detail that the diseases covered by the policy increased in an arbitrary fashion during our data period. We found that the demand-side policy increased firms' incentive to innovate. Specifically, firm-sponsored new clinical trials increased as much as 181% when covered by the policy. The impact of the policy was large and comparable to that of the ODA found in Yin (2008). For patients with these diseases, the results imply that reduced cost sharing brings a double benefit to them: it benefits patients statically by reducing their current medical spending and dynamically by increasing future treatment options. These effects are in fact as intended by the policy. In 2015, the government extended the number of eligible diseases for reduced cost sharing to more than 300 diseases. Our results suggest that development activities for these diseases will also increase in the near future.

Our results also indicate that the policy had a larger effect on later-phase trials. One interpretation of the result is that reduced cost sharing encouraged firms to conduct additional development on existing drugs and devices that had been shelved due to limited profitability, but the incentive was not strong enough for firms to initiate an entirely new development. For the latter purpose, an alternative form of innovation policy may be necessary.

Overall, our results imply that reduced patient cost sharing can have a large impact on firms' incentive to innovate, and thus, it should be considered as an important part of the innovation policy that aims to encourage R&D in markets with limited profit potential. An unanswered policy issue of critical importance is, of course, how to allocate resources between supply-side and demand-side policies to promote innovation and ultimately improve welfare. This would be an important area of future research.

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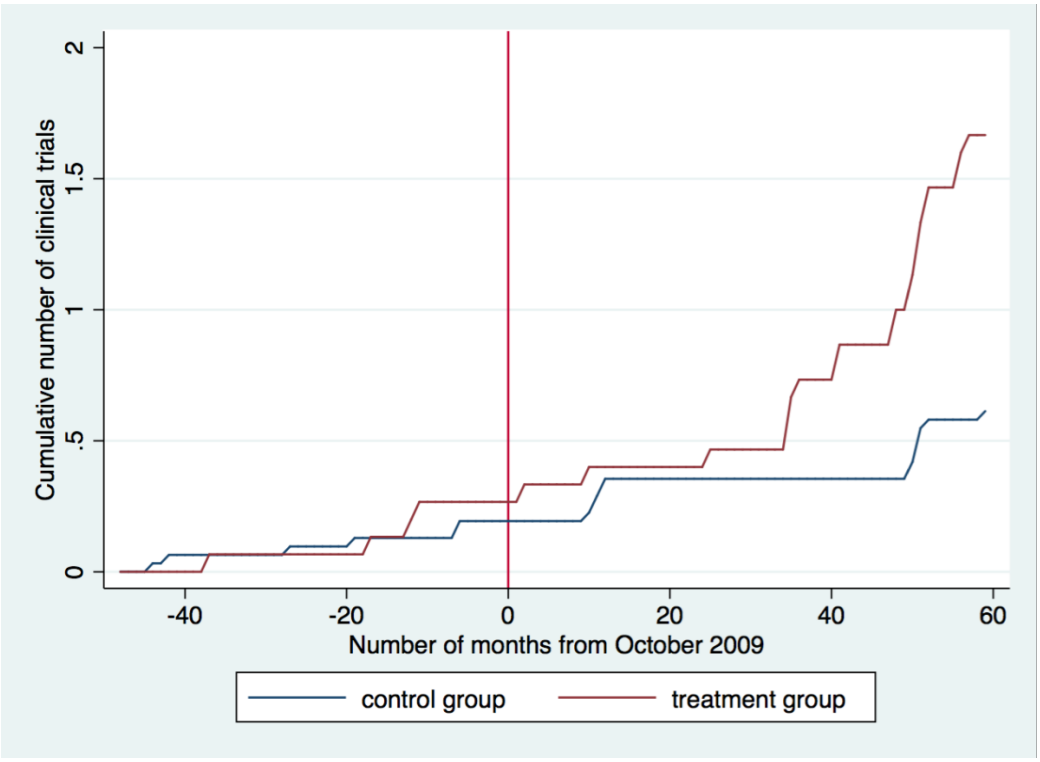

Figure 1: Cumulative number of clinical trials per disease over time.

Note: T = 0 corresponds to October 2009.

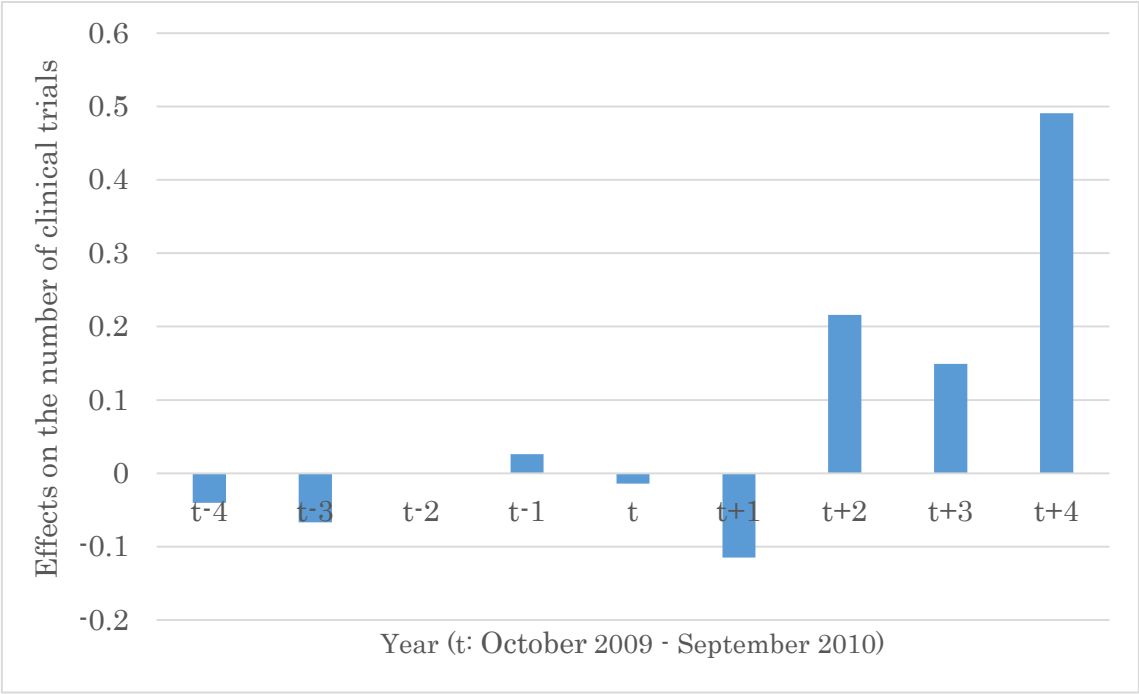

Figure 2: Effects of patient cost sharing on clinical trials by year

Note: The bars show the point estimate from Table 4.

Variables	Obs.	Mean	Std. Dev.	Min.	Max.
Clinical trials	414	0.106	0.470	0	7
Market size (in 10,000 patients)	414	0.484	1.124	0.002	6.630
Phase3 clinical trials	414	0.048	0.274	0	4
Phase2 clinical trials	414	0.036	0.223	0	3
Phase1 clinical trials	414	0.010	0.098	0	1
Physician-led trials	414	0.048	0.345	0	5
Firm-sponsored trials	414	0.058	0.244	0	2

Table 1: Summary statistics

	1	2	3	4	5
Variables	All clinical trials	Firm-sponsored trials	Physician-led trials	Firm-sponsored Phase 3	Firm-sponsored Phase 2
POST	0.166	0.157**	0.012	0.063	0.078**
	(0.105)	(0.062)	(0.069)	(0.041)	(0.032)
Grants	0.121	0.083	0.031	0.044	0.051
	(0.095)	(0.060)	(0.065)	(0.034)	(0.033)
Disease FE	YES	YES	YES	YES	YES
Year Dummy	YES	YES	YES	YES	YES
Observations	414	414	414	414	414
No. of diseases	46	46	46	46	46
R-squared	0.213	0.251	0.178	0.188	0.180

Standard errors collected for clustering at the disease level are in parentheses.
*** p<0.01, ** p<0.05, * p<0.1

Table 2: Results from the base model (Equation 1)

	1	2	3	4	5
Variables	All clinical trials	Firm-sponsored trials	Physician-led trials	Firm-sponsored Phase 3	Firm-sponsored Phase 2
POSTTREND	0.080	0.054**	0.026	0.017	0.033**
	(0.055)	(0.026)	(0.038)	(0.018)	(0.014)
Grants	0.111	0.082	0.021	0.046	0.048
	(0.100)	(0.061)	(0.071)	(0.035)	(0.032)
Disease FE	YES	YES	YES	YES	YES
Year Dummy	YES	YES	YES	YES	YES
Observations	414	414	414	414	414
No. of diseases	46	46	46	46	46
R-squared	0.227	0.264	0.183	0.188	0.208

Standard errors collected for clustering at the disease level are in parentheses.

*** p<0.01, ** p<0.05, * p<0.1

Table 3: Results from the linear post-trend model (Equation 2)

	1
Variables	All clinical trials
dt-4	-0.040
	(0.120)
dt-3	-0.067
	(0.087)
dt-1	0.026
	(0.134)
dt	-0.014
	(0.106)
dt+1	-0.115
	(0.083)
dt+2	0.216**
	(0.109)
dt+3	0.149
	(0.143)
dt+4	0.491
	(0.525)
Grants	0.120
	(0.097)
Disease FE	YES
Year Dummy	YES
Observations	414
No. of diseases	46
R-squared (overall)	0.238

Standard errors collected for clustering at the disease level are in parentheses.

*** p<0.01, ** p<0.05, * p<0.1

Table 4: Results from the “dynamic” model (Equation 3)

	1	1'	2	2'
Variables	All clinical trials	Marginal effects	Firm-sponsored trials	Marginal effects
POST	0.792	0.084	2.780**	0.154**
	(0.735)	(0.079)	(1.137)	(0.077)
Grants	14.915***	1.585***	13.818***	0.768***
	(0.367)	(0.212)	(0.541)	(0.205)
Reduced cost sharing	0.331	0.035	-0.978	-0.054
	(0.627)	(0.067)	(1.079)	(0.062)
Market size	-0.046	-0.005	0.093	0.005
	(0.177)	(0.019)	(0.175)	(0.010)
Year Dummy	YES		YES	
Observations	414		414	
No. of diseases	46		46	
Pseudo R-squared	0.174		0.152	

Standard errors collected for clustering at the disease level are in parentheses.

*** p<0.01, ** p<0.05, * p<0.1

Table 5: Results from the Poisson model (Equation 4)

Appendix A1: Data construction

This appendix summarizes how we constructed our clinical trials data. We used three public registries, that is, Japic Clinical Trials Information, UMIN Clinical Trials Registry, and JMACCT Clinical Trials Registry. We searched the databases with a list of search words (please see below) from April 8 to April 24, 2015.

Background of the databases

In September 2004, the major medical journals[29] announced their editorial policy, which indicated that studies involving clinical trials can be submitted for publication only if these trials were registered in a publicly available database[30]. In January 2005, international and regional pharmaceutical industry associations issued a statement on their joint position on the transparency of clinical trials[31]. From late 2004, the WHO launched the International Clinical Trials Registry Platform and started facilitating "the establishment of a network of international clinical trials registries." In line with this global trend, the three aforementioned Japanese registries were established in 2005.

The Japanese government's guideline on clinical research[32] became effective from April 2005. The guideline stated that the "heads of any clinical research organization are encouraged to disclose their plans and results of clinical research." The use of the word "encouraged" may imply that there was no strict obligation on researchers. However, when we conducted an interview with representatives from the UMIN CTR, they stated that researchers were "practically obliged to" register their research in at least one of the three registries. In addition to this "practical" obligation, there had been the aforementioned publication requirement of internationally recognized journals. Hence, it is highly likely that after April 2005, most of the clinical trials in Japan have been registered in one of the registries.

Screening relevant clinical trials from the databases

The three databases had search systems. In an attempt to find all the relevant clinical trials on the 47 intractable diseases, we used a number of search words for particular diseases. For example, when we searched for clinical trials of the POEMS syndrome, we used "Fukase," "POEMS," "monoclonal," and "Takatsuki" as search words[33].

However, the results sometimes included irrelevant clinical trials. We scrutinized each clinical trial to exclude apparently irrelevant ones. We also ruled out clinical trials that were only about a broader concept of an intractable disease. For example, when we searched for research on the homozygous type of the familial hypercholesterolemia, we used the term "familial hypercholesterolemia." However, the search included results on familial hypercholesterolemia that did not clearly mention whether it was a homozygous or heterozygous type. Thus, we ruled out such results. As for research that was aimed at

[29] The Committee consists of Lancet, JAMA, and other internationally recognized medical and pharmaceutical journals.

[30] http://www.icmje.org/news-and-editorials/update_2005.html (Accessed January 26, 2016).

[31] http://www.ifpma.org/ethics/clinical-trials-disclosure.html (Accessed January 26, 2016).

[32] http://www.mhlw.go.jp/general/seido/kousei/i-kenkyu/rinri/0504sisin.html (in Japanese. Accessed January 26, 2016).

[33] Since the websites are in Japanese, we typed in the keywords in alphabets and Japanese. We typed in the search words in the "disease/condition" and "free keyword" boxes of the database.

dealing with complications of the intractable disease, we included them in our data set as long as there was a clear mention of the intractable disease's name.

Based on the results at this point, we set a refined concise version of the search words list[34]. We searched the websites again with this list and scrutinized the results in the same way as we did in the initial screening.

In the results we acquired, we had the drug or pre-product code names of the relevant research. We typed in these names in the search systems, and obtained additional information. In earlier phases of the clinical trials, the name of the target disease was not clearly mentioned sometimes, but instead, a name of a broader concept of the disease was in the description. As long as the later stage(s) of the clinical trial of the same drug was about intractable diseases, we added such earlier stage(s) of the clinical trials to our final data set.

Constructing variables used in the analysis

We defined the variables used in the analysis in the following way.

Clinical trials: In this paper, we focus on the clinical trials that aim to receive the manufacture and sales approval of the government. However, the public registries contain other forms of research in the database. In the UMIN CTR and JMACCT CTR databases, we classified research as a clinical trial if it is clearly mentioned. The Japic database had no clear information on whether the research was a clinical trial. Thus, we classified the research as a clinical trial if the research satisfied the following three conditions: (1) its study type was interventional, (2) it specified a trial phase, and (3) its primary sponsor was a pharmaceutical company.

Trial start date: Trial start dates of most of the research were obtained from the databases directly. When the date was not disclosed in the database, we directly contacted the firm for the date. Fortunately, all firms provided us with the information under the agreement that we do not publicly disclose it.

Trial phases: We counted different phases of the same drug/device as separate trials. However, when multiple clinical trials existed for the same drug/device in the same phase, we counted them as one trial[35].

Firm-sponsored versus physician-led trials: The databases had information on the institution that was financially responsible for the research. With this information, we identified whether the research was initiated by a sponsor firm or was physician-led.

Market size: We used following four sources to obtain the market size of the diseases: Japan Intractable Diseases Information Center, documents on designated intractable diseases by the MHLW, a document on eating disorder issued by the MHLW[36], and the webpage of the WHO Kobe Centre[37].

[34] The list of search words for each disease is available from the authors upon request.
[35] The results were similar when we counted them as separate trials.
[36] http://www.mhlw.go.jp/shingi/2009/01/txt/s0130-4.txt (Accessed January 25, 2016).
[37] http://www.who.int/kobe_centre/mediacentre/high_blood_pressure_faq/ja.

Appendix A2: Rare and intractable diseases included in the analysis.

Disease name	Number of patients	Reduced cost sharing
Multifocal motor neuropathy (MMN)	400	0
POEMS syndrome	340	0
Syringomyelia	3000	0
Peroxisomal disorders	20	0
Progressive multifocal leukoencephalopathy	50	0
Late-onset lymphedema	4500	0
Addison's disease	2000	0
Pseudohypoparathyroidism	400	0
FGF23-mediated hypophosphatemic rickets/osteomalacia	50	0
Thyroid hormone resistance	3000	0
Hemolytic anemia (AIHA, PNH)	3000	0
Thrombotic thrombocytopenic purpura (TTP)	1100	0
IgA nephropathy	33000	0
Rapidly progressive glomerulonephritis	4800	0
Polycystic kidney disease	29000	0
Autoimmune hepatitis (AIH)	10000	0
Idiopathic portal hypertension (IPH)	900	0
Cystic fibrosis	50	0
Sjogren's syndrome	66300	0
Adult still's disease	4800	0
Allergic granulomatous angiitis	1800	0
Giant-cell arteritis	700	0
Alveolar hypoventilation syndrome	3000	0
Tuberous sclerosis	8000	0
Fibrodysplasia ossificans progressive (FOP)	50	0
Xeroderma pigmentosum	450	0
Primary lateral sclerosis (PLS)	175	0
Chorea-acanthocytosis	50	0
HTLV1-associated myelopathy	3000	0
Congenital ichthyosiform erythroderma	200	0
Primary sclerosing cholangitis	400	0
Chronic inflammatory demyelinating polyneuropathy	2045	1
Spinal muscular atrophy (SMA)	712	1
Spinal and bulbar muscular atrophy (SBMA)	960	1
Ossification of the ligamentum flavum	2360	1
Syndrome of abnormal secretion of prolactin	12591	1
Syndrome of abnormal secretion of gonadotropin	792	1
Syndrome of abnormal secretion of antidiuretic hormone	1900	1

Hypertrophic cardiomyopathy	3144	1
Restrictive cardiomyopathy	24	1
Mitochondrial disease	1087	1
Familial hypercholesterolemia (Homozygous type)	140	1
Lymphangioleiomyomatosis	526	1
Hypopituitarism	8400	1
Cushing disease	600	1
Acromegaly	3000	1