Competition, Public Funding and Innovation: The Case of the Pharmaceutical Industry

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Abstract

In this paper I analyze two different dynamics in the drug development process of the pharmaceutical industry. In the first part, I study the strategic reactions of firms to news of success from competitors at the development stage, and I estimate learning effects when a competitor is developing a technologically similar product. In the second part, I study the effects of private-public collaborations in the drug development process. I find that firms terminate their projects earlier after hearing news of success from a competitor suggesting that the competition effects are strong, except for cases when the competitor is working on a technologically similar project. In the later case, news of success from a technologically similar project decrease the termination rate. This indicates that the learning effects overcome the competition effects. For private-public collaborations, I find a strong positive correlation between project success and some government programs even after incorporating controls for innate project potential. By using a difference in differences estimator, I find that the overall effect of the introduction of the Biomedical Advanced Research and Development Authority (BARDA) program in 2006 on the production of new early-stage research projects might have been as large as twenty percent with high significance in the therapeutic markets that qualify for this program. Interestingly, there seems to be a negative effect on the success rates of projects that started after the introduction of the program, with a 0.7 reduction on average in the number of projects approved by therapeutic market. I hope that my results shed light on how economic factors within the pharmaceutical industry affect the number of drugs that are available for consumers.

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1 Introduction

The uniqueness of the pharmaceutical industry sets the stage for interesting strategic firm behaviors in the drug development process. When working towards the approval of a pharmaceutical project, firms encounter numerous hurdles to success, which leads to a very low probability of registering a product. Moreover, the costs that this process involves are considerable. In result, firms must determine whether it is in their best interest to continue a project they have started based on the results from their own trials and based on signals that originate from the competition. Furthermore, publicly funded grants and public-private partnerships influence firm behavior. Some government grants are designed to encourage research in certain therapeutic markets. Public-Private partnerships encompass a different set of deliverables that firms try to maximize, which could lead to different behaviors relative to projects with a purely profit-maximizing strategy.

The first objective of this paper is to analyze how information about competition influences firms' behaviors when deciding the fate of a drug development project. For this paper, two projects are defined as competing projects if they belong to the same therapeutic market. The pharmaceutical industry is unique because firms can partially observe their competitors' development projects before they enter the consumer market. This leads to competition effects from other projects developing at the same time. Using a probit model to calculate the probability of termination of a project in a given time period, I estimate the effects of the presence of competition in the development stage, news about a competitor's success, and how the size of the competitor affects those reactions. In addition, I include in my analysis the relative magnitude of learning effects related to competing projects that are developing similar technologies because this information can help a firm update their expectations of whether their technology is promising. That is, for projects using a chemical compound that has never been approved by the FDA, how do firms react to news from projects with a similar technology. In the context of this paper, similar technology is defined as having the same mechanism of action and target technology. The mechanism of action is the specific biochemical interaction through which a drug substance produces its pharmacological effect. Considering technological similarity

is relevant because a technologically similar success from a competitor can signal that the technology has the potential of being approved. This can lead to strategic responses by the competitors. By considering both of these forces, I replicate the findings of the current literature while incorporating the dimension of firm size into my analysis and considering a more representative sample of drug development projects in the industry.

The second objective of this paper is to understand how public-private collaborations influence the strategies and outcomes of development projects. I estimate the effect on project success rates from public-private partnerships. In particular, I assess the efficacy of government grant programs such as the Qualifying Therapeutic Discovery Project Program, the Small Business Technology Transfer (STTR) program, and collaboration contracts with the Biomedical Advanced Research and Development Authority (BARDA). In addition, I use a difference in differences estimator to show the effect of the introduction of the BARDA program in 2006 on the production of new projects and their respective success rates for the therapeutic markets that qualify for BARDA's contracts.

I find that competition has an adverse effect on the probability of continuation of a drug development project, and firm size of the competitor magnifies such an effect. When estimating the probability of termination, the number of competing firms currently developing in the same therapeutic market (i.e., developing drugs that are intended to treat the same disease) has a marginal effect of 0.0008 in the probability of termination in a given semester, while the number of registered competing projects has a marginal effect of 0.0019, with a p-value less than 1% in both cases. These results suggest an approximate increase of four percent in the probability of termination of a project for each competing project and a nine percent increase for each registered competing project relative to the base probability of termination in a given semester. Additionally, I find that learning effects from competitors' successes on technologically similar projects overcome competition effects and lead to an overall drop in the probability of termination. With a marginal effect of -0.0016 (p-value less than 1%) in the probit regression (7% decrease in the probability of termination), learning effects appear to have almost twice the

magnitude of the competition effects in the opposite direction when there is a registration from a competing project. Size of the competing firms also seems to play a relevant role, being both an intimidating factor to smaller firms and a signal to firms with technologically similar projects that a certain technology has potential due to continuing development and investment.

In my analysis of the impact of public-private collaborations, I find interesting results. Focusing on the BARDA program, the difference in differences estimator suggests an increase in research activity due to the introduction of this program. I estimate that 5.1 additional new projects per therapeutic market can be attributed to the 2006 introduction of BARDA. This is equivalent to a 20% increase in the number of new projects for BARDA-eligible markets from 2006 levels. This suggests that the BARDA program was very effective in incentivizing firms to start the development of drugs in eligible therapeutic markets. Nevertheless, when I consider the number of successful projects that were introduced each year I find a negative effect from the BARDA program. On average, treated therapeutic markets experienced a 0.7 decrease in the number of successful projects following the introduction of the program. I discuss some potential explanations for this pattern in section 5.3. Using a linear regression model with controls for innate potential, I provide evidence that in estimating the effect on success rates for projects receiving BARDA, SBIR or QTDP grants, there is a significant positive bias led by innate project potential.

2 Literature Review

2.1 Competitor's signals and strategic reactions:

Previous literature has looked into the effects of competition by considering competitors' projects targeting the same condition and competitors' drugs using a similar technology and has found contrasting results signaling that there are economic forces with opposite effects at play when making strategic decisions based on competitors' outcomes. In "Strategic R&D Investment Decisions in the Pharmaceutical Industry" (2015), Anita Rao analyzes the impact of competition on investment in development projects in order to evaluate the potential effects of

an expedited review process by the Food and Drug Administration in the United States. In her results, Rao finds evidence of a negative impact of competition on investment in a model that suggests that the probability of continuation of an R&D project in the pharmaceutical industry decreases with announcements of FDA approvals to competition products. On the other hand, Rao finds evidence that when the FDA rejects a project from a competitor, the probability of continuation of a firm's own project increases. Rao's methodology uses Phase 3 clinical trial data; therefore, looking into the dynamics of the industry by considering all phases of research in the clinical trial stage is of relevance to fully understand the effects of competition. For my paper I am interested in understanding not only how FDA approvals impact the probability of continuation, but also how the number of competitors in the research stage impact this probability. This allows us to understand how firms react to signals from competitors at earlier stages of research. In addition, I investigate how firm size from competitors interacts with the probability of termination.

In the working paper "Trials and Terminations: Learning from Competitors' R&D Failures" (2017), Joshua L. Krieger considers technology learning effects from competitors' failures for his analysis. This approach leads to contrasting results to the ones presented by Rao (2015). Krieger argues that given the uncertainty of whether a drug project will be approved or not, firms consider the failures or successes of their competitors to update their estimations of the probability of approval in order to make strategic decisions. Particularly, if a competitor's project has the same mechanism of action or shares other technological characteristics, firms will be more likely to terminate projects after learning of their competitor's failure. This suggests that the technology learning effect dominates over the competition effect. That is, firms will more likely terminate projects given their updated expectations of the probability of approval of their project after their competitor's failure even though they are also more likely to face less competition if their project reaches the market. Krieger finds that it is indeed the case that technologically similar project's terminations will lead to a higher probability of termination for a drug. Similar to Rao's methodology, Krieger focuses on a panel of drugs in Phase 2 clinical trials. I replicate his results by expanding the number of phases under consideration in my

sample, as well as by including interactions with firm sizes. In addition, I consider the number of competing projects using a similar technology as a variable to better understand the effects of success news and the effect of the presence of others investing in research on a similar technology, which might signal to the firm that the technology is promising.

In *"*Killer Acquisitions*"*, Cunningham et al. work with the same data set for the drug-indication level data as mine (2017). They present evidence for the magnitude of 'killer acquisitions' (when a company acquires a competitor to terminate their pharmaceutical projects). This strategic behavior by firms not only prevents competition from projects owned by other firms, but it also prevents market cannibalism. For their data, Cunningham et al. utilize the same data set as mine, Pharmaprojects from Pharma Intelligence. They complement their drug-indication level data with a privately-owned data set. However, they utilize a similar approach to mine in the merging of the data sets by using fuzzy string matching to overcome the difficulties created by inconsistencies and spelling mistakes in names for Pharmaceutical companies and drugs. By using publicly available clinical trials data instead of a privately-owned data set, I want to understand how well my data set compares to the privately-owned data set. This can help future research into the field have lower entry costs. I further discuss the improvements to my data set I made using publicly available information in section 3.2.

My results and analysis provide further evidence for the competition effects and technology learning effects evaluated in "Strategic R&D Investment Decisions in the Pharmaceutical Industry" (Gao, 2015) and "Trials and Terminations*"* (Krieger, 2017). Furthermore, I also present some results that investigate the effect of the size of the firm's competitors and the phase of development of competitors in the clinical trials stage.

2.2 Public-private partnerships, strategic behavior and project outcomes

When studying the effect of government funding and public-private partnerships, most of the existing literature has focused on spillovers on private-sector patenting based on publicly funded

research (Azoulay, et. al., 2018; Cockburn and Henderson, 1996) and has compared the magnitude of research spillover effects depending on the source of funding (Furman et. al., 2016). However, little attention has been given to the effect of public-private collaborations and public interventions during the clinical trials stage, which is fundamental in understanding whether these programs are leading to more drugs being available to the final consumer. While spillover effects in the early discovery stage lead to an increase in the number of patents, it is more relevant to understand how these partnerships increase the chances of a project being successful.

In "Public R&D Investments and Private-sector Patenting: Evidence from NIH Funding Rules" (Azoulay et. al., 2018) the authors present evidence of a positive effect of grant funding from the National Institutes of Health (NIH) on patenting by pharmaceutical and biotechnology firms. By relying on bibliometric data, this paper finds a net 2.7 increase in patents for every 10 million dollar boost in NIH funding. To calculate the economic effect of such investments, the authors estimate the potential value of each patent. While their approach is useful in shedding light on the effect of public grants on the discovery process, it does not explain whether continuing public investment from the NIH, HHS and other government agencies through private-public partnerships during the clinical trials stage further improves the prospect of success for a particular development project.

In "Public-Private Interaction and the Productivity of Pharmaceutical Research", Ian Cockburn and Rebecca Henderson (1997) examine the impact of publicly funded biomedical research on the in-house research of the for-profit pharmaceutical industry. Their research question is similar to that of Azoulay et. al. (2018), in measuring the connectedness of the for-profit research industry and the publicly funded research projects by considering co-authoring. For their methodology, unlike Azoulay et. al (2018), they consider data from drug development projects. Their empirical method, however, is more qualitative in nature and is based on a limited sample of 21 drug development projects that were successful. For this paper, I utilize a sample of 38,240 projects in the drug development stage.

No other paper has analyzed the effect on the production of new projects and industry-wide success rates of clinical-trial-focused programs, such as the BARDA program. I use a difference in difference estimator to approximate these effects. This approach can help us appreciate the impact on the industry dynamics of these interventions, as well as their possibly unintended consequences.

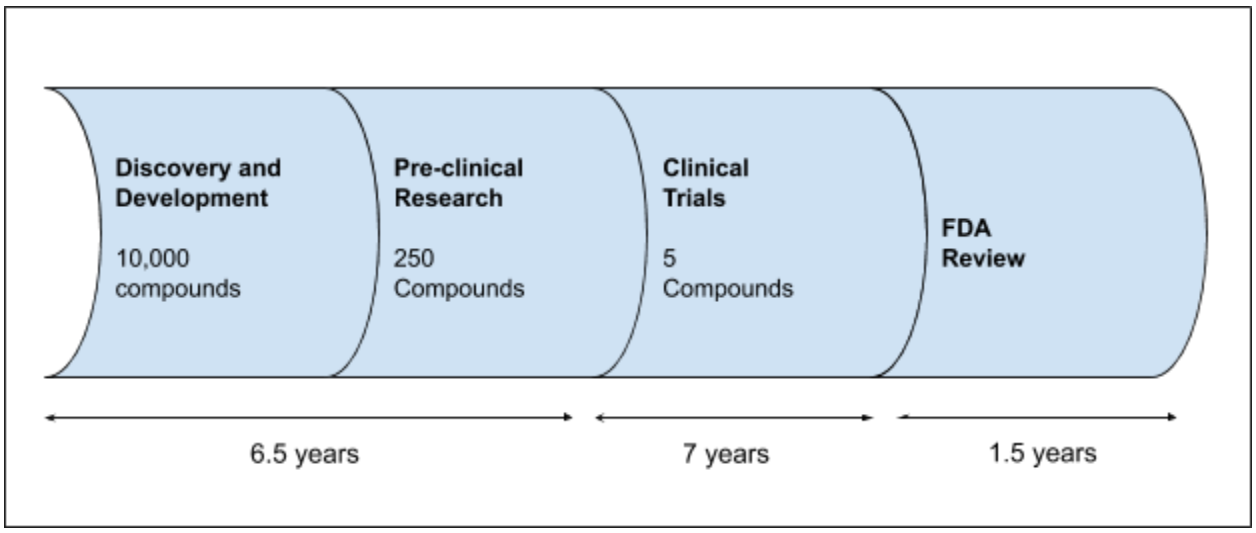
3 Empirical Setting

3.1. The drug development process

The United States is the largest pharmaceutical market by far. In 2017, the US pharmaceutical market size was 457.0 billion dollars, while the second largest market, China, accounted only for 84.6 billion dollars (IQVIA, 2018). Therefore, for most pharmaceutical projects, approval by the US Food and Drug Administration (FDA) is one of their main goals, regardless of the country of origin of the parent company. I begin this section by discussing the drug development process, using the United States as an example, and then I proceed by explaining the importance of globalization in the industry.

In the United States, the drug development process has 4 stages before a drug is approved by the FDA to reach the market (FDA, "The Drug Development Process", 2019). The first stage, discovery and development, is where thousands of compounds (on average 10,000) are screened by researchers to identify potential candidates to treat certain conditions. Once a set of promising compounds has been identified, a series of basic experiments help determine whether those compounds are viable for the treatment of a condition and how they compare to existing drugs. In the second stage, preclinical research, researchers try to understand the toxicity and safe dosage of the most promising variations of a compound before the drug is tested on humans. At this stage experiments are done *in vitro* and *in vivo*, which are regulated by the FDA to be valid for approval for human clinical trials. These experiments do not tend to be very large, and represent smaller costs relative to other stages (FDA, 2019).

Figure 1: The drug development process



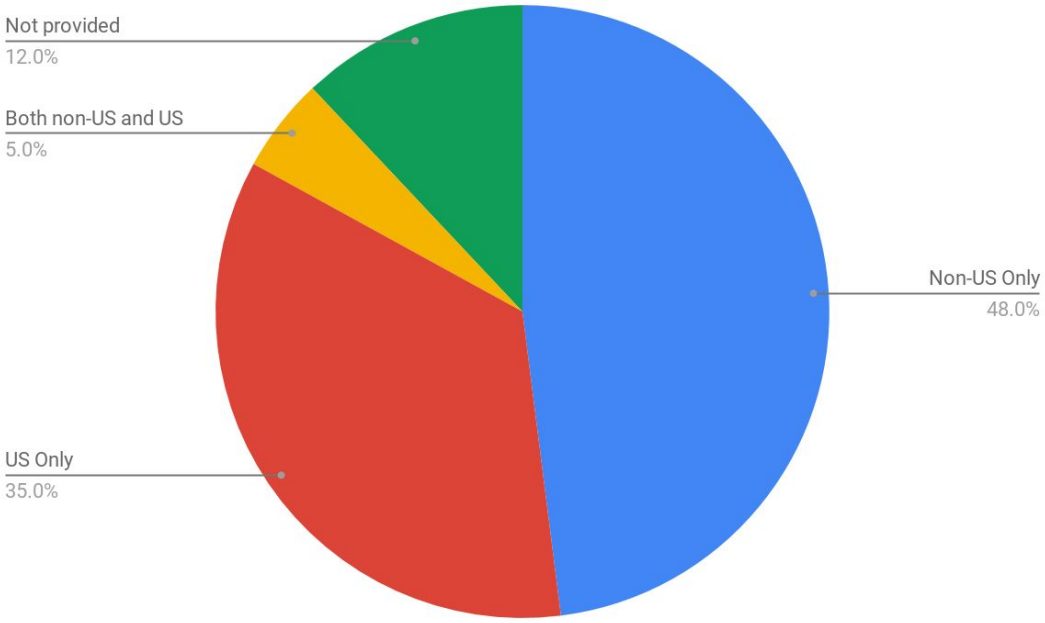
If a drug is still considered viable after the first two stages, clinical trials are allowed to begin as part of the third stage. At this stage researchers are concerned with the interactions of the drugs with the human body and plan studies with human participants. This stage consists of 4 phases, each with an increasing cost and size. The first phase of the clinical trials stage which lasts several months involves 20-100 people, and the main concern is dosage and safety. At this phase each study has an average cost of 4 million dollars. The second phase which can last up to 2 years involves several hundred people with the targeted disease and costs on average 13 million dollars per study. The efficacy and safety of the drug is tested at this phase. The third phase consists of increasingly larger scale versions of the trials from the second phase. It can take up to 4 years on average and only around 6% of the drugs that start these clinical trials get to the following phase. Each study at this phase has an average cost of 20 million dollars, with some studies reaching hundreds of millions of dollars. After a drug goes through phase 3 trials, in the fourth stage of the drug development process, a FDA committee evaluates the results and evidence from the trials and determines whether the drug is safe for marketing to the general public. Phase 4 clinical trials continue after registration with the FDA to monitor unexpected side effects of the drug as well as long term effects (Sertkaya, Aylin, et al., 2016; Adams, C. P. and Brantner, 2010; FDA, 2019).

3.2. Global dynamics in the drug development process

The drug discovery process in most countries mirrors that of the United States by having a discovery, preclinical and a clinical phase before approval by the corresponding national agency. For instance, the European Medicines Agency, which supervises drug approval in the European Union (which as a block, is a bigger market than China's) in coordination with national agencies, has the same structure as the United States in terms of stages and clinical trial phases (Nathalie Bere, 2015). While there are differences in the review process, pharmaceutical projects can utilize the same clinical trials data to apply for approval in United States and the European Union (FDA, Human Subject Protection, 2008). Furthermore, the Mutual Recognition Agreement (MRA) between the United States and the European Union allows drug inspectors to rely upon information from drug inspections conducted within each other's borders. Hence, European and American based projects tend to work towards the approval by both agencies in parallel, without additional significant costs (FDA, Mutual Recognition Agreement, 2019).

Most projects that submit clinical trial data to the FDA did not undergo all of their clinical trials in the United States (NIH, Clinicaltrials.gov, 2019). Figure 2 shows that only 35% of clinical trials in the ClinicalTrials.gov data-base were based in the United States. The FDA accepts international and foreign trials as long as they meet or exceed certain ethical standards, and they are subject to inspections and site visits. The share of these trials from emerging countries has been growing over the years. The increase in non-US trials in FDA applications has been fueled by lower costs, difficulty in recruiting patients in the US, and the growth of the pharmaceutical industry in other countries (Thiers, 2006; Ayalew, 2012). It is therefore very relevant to consider an open, global system for this analysis. A registration of a drug candidate abroad is a relevant factor in determining potential competition in the consumer market. For my analysis, I use data on international drug development projects instead of limiting my focus to the United States.

Figure 2: Clinical trials submitted to the FDA by origin



I focus on data from the clinical trials stage, since this is the costliest chapter of the drug development process, and it is instrumental in defining whether a drug development project will reach the market. A drug candidate that starts the clinical trials stage encounters numerous obstacles to completion (Sertkaya et al., Examination of Clinical Trial Costs and Barriers for Drug Development, 2014). The high financial cost of the complete clinical trial process is around 171 million dollars according to some estimates (Adams & Brantner, Spending on new drug development, 2010) and 339.3 million dollars according to a more recent study (DiMasi et al., Innovation in the pharmaceutical industry: new estimates of R&D costs, 2016). Lengthy timelines and the difficulty to recruit participants for studies often lead to the termination of trials before they are completed (Sertkaya et al., 2014).

I also investigate how the size of the competitors influence firm behavior. To accomplish this, I consider how the presence of competing firms in the clinical trials stage, as well as news from their success, influences the probability of termination depending on the sizes of the competing firms. Moreover, I consider technology learning effects (Krieger, 2017) and phase of

development of the competitors in order to understand more broadly the dynamics of competition at this stage.

3.3. Public-private collaborations in the drug development process

Government funding and grants for R&D activities in the pharmaceutical industry are common around the world. The United States, Germany and Japan are some examples of countries that invest heavily in pharmaceutical R&D activities (ABPI, 2016). Due to the global interconnectedness of the market, as discussed above, government funding should be considered in a global setting. In this paper I look into the effect of some grant and contract programs from the United States, using a global panel of projects. My focus on US government programs is due to the limitations of my data set. Nevertheless, the US still represents 60% of R&D investment worldwide (ABPI, 2016), so these grant programs are possibly the most relevant in a global context. The federal government funds 33% of the medical research conducted in the United States, while the private industry's share amounts to 58% (Dorsey et al., 2010). Hence, public funding represents a large proportion of the drug development funding sources in the US. In addition, public-private collaborations such as the Qualifying Therapeutic Discovery Project Program, the Small Business Technology Transfer (STTR) program, as well as patenting agreements have become very prevalent in the drug discovery process.

Most of the research funded by the federal government focuses on the discovery stage of the drug development process, led primarily by the National Institutes of Health (Institute of Medicine, Current Model for Financing Drug Development: From Concept Through Approval, 2009). At this stage, the federal government represents the vast majority of research funding. However, at later stages, which are also associated with higher development costs, the private industry takes the primary role (Dorsey et al., Funding of US biomedical research, 2003-2008., 2010). The federal government focuses mostly on supporting small businesses during the clinical trials, while it also directs funds for grants to projects whose targets are therapeutic indications that fall within the list of priorities of the distinct institutes that compromise the NIH or that pertain to national security (i.e., QTDP, STTR/SBIR, BARDA programs).

For this paper I focus primarily on the effect of the Small Business Technology Transfer (STTR/SBIR) program, the Qualifying Therapeutic Discovery Project Program (QTDP), and the Biomedical Advanced Research and Development Authority (BARDA) collaboration program. The first two programs offer either grants or tax incentives to small businesses trying to enter the market after developing promising molecules. The BARDA program is part of the US Department of Health and Human Services (HHS) Office of the Assistant Secretary for Preparedness and Response and was created to assist national security goals. This program consists of a more hands on collaboration that includes funding and technical assistance through a contract with the HHS (BARDA, Broad Agency Announcement, 2019).

Table 1: Number of projects that reached the clinical trial's stage by grant status

Clinical Trials	SBIR/STTR	QTDP	BARDA
Did not reach	296	453	12
Reached	159	946	77
Total	186	645	89

The STTR/SBIR program is intended for firms with less than 500 employees, and funding is awarded to projects that are deemed to have significant technological potential. As stated in the program's objectives: "by reserving a specific percentage of federal R&D funds for small businesses, SBIR protects the small business and enables it to compete on the same level as larger businesses. SBIR funds the critical startup and development stages and it encourages the commercialization of the technology, product, or service, which, in turn, stimulates the U.S. economy." Hence, the projects supported by this grant have inherent technological potential, but are owned by firms that would otherwise have a very small probability of taking the project into the market. Central to the STTR/SBIR program is the requirement for the small business to formally collaborate with a research institution, which might have profound effects in strategic behaviors, as well as spillover effects. Financial support from this program is capped at $252,131 during the first stage of collaboration, and if there is initial success, the cap is increased to $1,680,879 as of 2018. However, no funds are allocated to fund the final stages of the

commercialization effort, so most of their funding in the pharmaceutical industry is limited to the pre-clinical stages, which as discussed earlier, represent the smallest financial burden in the drug development process as compared to clinical trials. Therefore, most firms benefited by this program must find alternative sources of funding or other investment partners to take their projects into the clinical trial stage (Small Business Association, About SBIR, 2019).

The Qualifying Therapeutic Discovery Project Program was enacted as part of the Patient Protection and Affordable Care Act of 2010. This program provides funding in the form of a tax credit or a grant, depending on whether the firm is profitable or not. In addition, a requirement to receive this grant is that the firm has less than 250 employees. The grant amounts to 50% of the costs of research for a given project with a cap of 5 million dollars per tax year. The cap is above the average yearly cost of Phase 1 trials, about half the average yearly cost of Phase 2 trials, and about a quarter of the average yearly cost of Phase 3 trials. Therefore, the potential financial support from this program is significant (NIH, QTDP Program, 2010). Nevertheless, the majority of the projects benefited by this grant received funding prior to entering the clinical trial stage, and the average grant amount was much smaller than 5 million dollars (IRS, Qualifying Therapeutic Discovery Project Credits and Grants, 2010).

The BARDA program, on the other hand, provides a more complex partnership structure that includes other forms of support in addition to funding. As stated in the program's objectives: "BARDA supports the transition of medical countermeasures such as vaccines, drugs, and diagnostics from research through advanced development towards consideration for approval by the FDA and inclusion into the Strategic National Stockpile". Therefore, the focus of this government collaboration is in achieving a product registration. This results in an active partnership that not only includes the discovery stage, but it also further extends into the clinical trials stage (BARDA, 2019). This is extremely relevant when considering the probability of success since the most challenging stage in the drug development process is the clinical trials stage. Another relevant characteristic of BARDA is that it only targets projects in therapeutic markets that are relevant to the national security of the United States. The availability of funds from this program in certain markets can produce an incentive for firms to develop products in

the therapeutic markets targeted by the program. I analyze this effect through a difference in difference estimator, exploiting the introduction of the BARDA program in December 19, 2006, through the Pandemic and All-Hazards Preparedness Act by the US Congress.

It is important to note that while the QTDP and STTR/SBIR are programs that are only available to small firms, due to the existence of partnerships among pharmaceutical firms, other partners of various sizes are benefited by these programs (Appendix B shows the distribution of grantees and benefited partners by firm size).

3.4. Data

I construct my dataset using Pharmaprojects from Pharma Intelligence, a privately-owned database that has been used by other papers (Cunningham et al., Killer Acquisitions, 2017; Branstetter et al., Starving (or Fattening) the Golden Goose?, 2014). This dataset includes 69,537 drug candidate projects with specific information relating to pre and post-clinical trial stages, patent applications, registration and approval dates, launch into market statistics and termination announcements. It also includes relevant dates to the development cycle of a drug, such as entry into the distinct clinical trial stages and registration dates. In addition, it keeps track of the condition markets for which the drug has been tested, the drug's target (which is an indicator of the type of technology being used) as well as whether the compound being tested has ever been approved before (which can allow us to focus on the projects with the most uncertainty). Given the size of the dataset, and the number of global firms involved, this dataset also allows us to understand the relative size and market share of a pharmaceutical company within the research industry and the specific condition's market. Information about clinical phase entries is limited for this data set, so supplementing it with additional clinical trials data is necessary for an analysis that involves interactions with competitors' phase of development.

3.5 Sample construction and analysis data for competition and learning effects

To measure the effect of competition dynamics on termination rates, I focus on the largest medical condition markets in terms of drug research within the Pharmaprojects database, which

include Alzheimer's disease, asthma, rheumatoid arthritis, type 1 diabetes, type 2 diabetes, unspecified diabetes, HIV/AIDS, psoriasis, chronic obstructive pulmonary disease, obesity, multiple sclerosis, hepatitis-C virus infection, Parkinson's disease, cerebral ischaemia, depression, osteoporosis, schizophrenia, Crohn's disease, atherosclerosis, inflammatory bowel disease, and osteoarthritis. For the 20 condition markets I consider in my analysis, I have data on 14,161 drug projects. This restriction is due to the need to process raw data for each therapeutic market in order to extract the relevant dates for each project.

I supplement my data using clinical trials public information from the National Institutes of Health's clinicaltrials.gov database. This set contains data on 277,765 research studies from all 50 states and 204 countries, whether completed, terminated or continuing phase 1, 2, 3 and 4 trials. Importantly, the data includes the condition for which the drug is being tested and the study start date and completion date, which I use to track the history of a drug candidate within the clinical trials stage and improve the quality of our data from Pharmaprojects. Since only after the 1997 Food and Drug Administration Modernization Act were firms required to make clinical trial information publicly available for drugs, my data set for clinical trials mostly pertains to drugs starting after this time period. I was able to match 17,600 clinical trials to 4,064 Pharmaprojects entries using only the top 20 indications in the Pharmaprojects data set and extracted the relevant dates to update them and have a more complete mapping of the life cycle of these drug development projects. After processing the matched data, I complemented and updated 1,086 drug development projects out of 4,681 projects in my final subset of projects that entered the clinical stage. In addition, for the projects where I was uncertain whether they reached clinical trials, I was able to corroborate that 1,370 of them had no trials associated with them in the National Institute of Health's database.

For the drug projects that have multiple conditions associated to them, I generate an entry per condition with the specific dates associated to that particular condition because a single project might be competing in multiple therapeutic markets at the same time. I use flexible string matching to associate the development dates with particular conditions in the cases where multiple diseases are associated with a single drug project in order to have the relevant dates for

a given market. For my analysis, my units of observation are the individual drug projects for a particular condition and at a particular semester with variables on whether they were in development, registered or terminated during that semester as well as other relevant status updates in their life cycle.

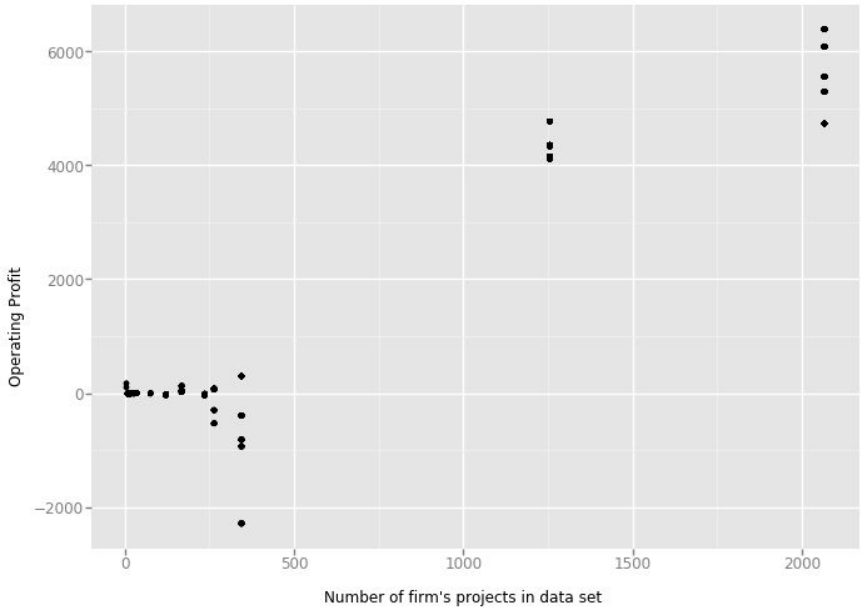
I also include the variable "new chemical entity" (NCE) which indicates if a drug contains no active molecule that has been approved by the FDA in any other application at the time that the project started. In the Pharmaprojects data set, projects considered as new chemical entities represents 61% of the data. This variable is relevant for the analysis of the competition dynamics, especially for technology learning effects, since I am interested in measuring the effect of news that could indicate that a given technology has higher potential of being approved by the FDA. NCEs have a different approval process than those compounds that have been approved before. The inclusion of this variable allows me to focus my analysis on those projects that face the most uncertainty on whether the project will reach the market.

The main variables that I construct to measure competition effects and technology learning effects are the count of competing firms developing on a given semester (overall and by phase in the clinical trials stage), the count of competing firms developing a product with the same target technology, and the count of non-competing firms (developing for a different condition) developing a product with the same target technology. This is with the intention of being able to understand the competition effects and the learning effects that impact the probability of a project being terminated. I define competition as being in the same therapeutic market and similar technology is defined based on the target of the drug.

In order to have a measure of firm size, I consider the number of pharmaceutical projects being developed under their name in the Pharmaprojects data set. I use this metric as a control for a project's originator firm size in my regressions. Using number of projects developed as a measure of firm size incorporates the experience of the firm in the research and development market. In addition, it also serves as a proxy for other variables such as firm revenue and operating profit as shown in figure 4. I generated variables for firm revenue and operating profit

using data from the Compustat data-base. One limitation of using financial data as a metric for firm size (as an alternative to my metric) is that such data is mostly available for publicly traded companies, leading to a lack of data for many small and private businesses in my data set.

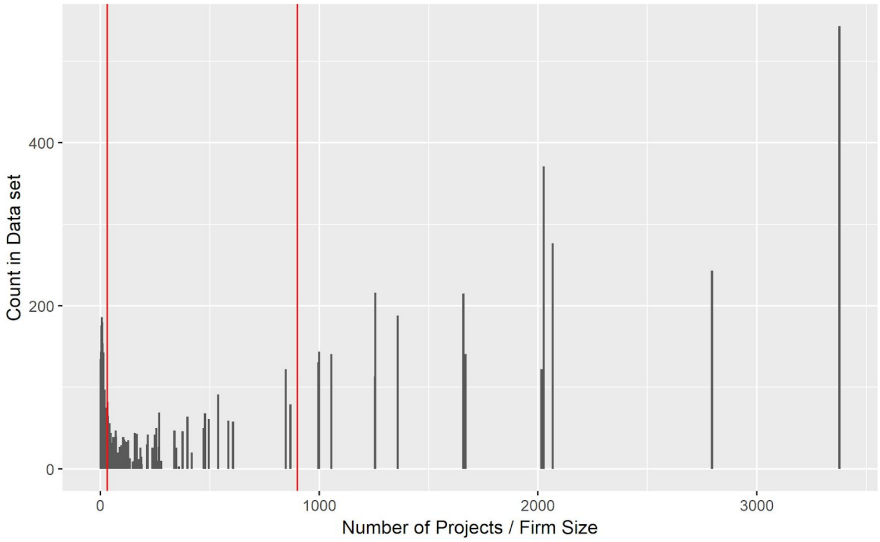
Figure 4: Number of projects in data-set and operating profit by firm



In order to consider the effect of the competition's firm size, I require a metric that aggregates my measure of firm size of the various competitors of a drug development project. Since any given project has multiple competitors at a given point in time and my analysis involves discrete time intervals (semesters) this aggregation is necessary since the multiple competitors of a project have different firm sizes. One way of doing so is to categorize the competitors' size in brackets. This can allow us to subdivide the number of competing projects (and news of success) by the firm size of the competitors into a finite number of categories and stratify the impact of news of success and presence of competitors using these categories. I group firms using quantiles in order to have an even distribution of my data among 3 size categories which I designate as small, medium and large. It is relevant to note that while I use this categorization to create a measure for competitor's firm size, I still use the number of projects owned by the originator

variable as a control for a firm's own size (since there is no need to use brackets or any aggregation method in that case).

Figure 3: Frequency histogram of firm sizes and thresholds used for competitor's firm size variables



Frequency distribution of the number of mentions in our data set by firm. The first and second red lines denote the 33% and the 66% quantiles, respectively. These quantiles were used as thresholds to define small, medium and large firms.

3.3. Sample construction and analysis data for public-private partnerships

In contrast to the previous sample construction, to analyze the effect of government funding and public-private collaborations on success rates I do not restrict my sample to the top 20 indications. Instead, I include the 69,537 drug candidate projects in the Pharmaprojects set. My unit of observation is the drug discovery project, and I have data on whether that project received a US government grant as well as the type of grant (BARDA, STTR/SBIR, QTDP). To generate the variables pertaining grant and public-private partnership status, I use Regex string matching to extract information from some manually entered fields that summarize the history of certain events in the project's life cycle. I define firm size in the same way as Figure 3 and include indicator variables for whether the project received a QTDP grant, a SBIR/STTR grant or was the result of a BARDA collaboration.

To control for project potential, I code and generate variables pertaining to the project's therapeutic market, firm size, and project start and end years. In addition, I generate the following variables as controls for potential of being approved by the FDA: number of FDA approvals in the project's therapeutic market; number of projects with a similar technology; number of projects with a similar technology that achieved registration; and an indicator for drug-likeness known as the Lipinski's rule of five. A compound that is drug-like, meets certain chemical characteristics that increase the chances of a drug being absorbed and utilized by the human body. While this heuristic is not deterministic on the potential for a drug, it is widely used in the pharmaceutical industry as a metric for approval potential, making it relevant as a control for selection bias in the process of selecting awardees for a grant or collaboration contract.

3.6. Sample construction for difference in difference estimator for the effect of BARDA

One interesting characteristic of BARDA is that eligibility is conditional on being a project within one of the following therapeutic market categories: chemical, biological, radiological and nuclear defense vaccines (this category includes therapeutic markets such as anthrax, smallpox, Ebola, among others); antitoxins and therapeutic proteins (this category includes several viral hemorrhagic fevers, and various other infectious diseases that are widely spread); antibacterials; radiological/Nuclear Threat Medical Countermeasures (this category makes several types of cancer markets eligible); Influenza and Emerging Infectious Diseases (IEID) vaccines; among others.

To analyze the effect of BARDA in the qualifying therapeutic markets, my unit of observation is therapeutic markets by year. I generate a count of new projects by year for each therapeutic market as well as a count of projects that were successful in that therapeutic market that started that year. Using the therapeutic classes targeted by BARDA and considering historical awards, I identified 65 therapeutic markets, out of the 210 largest therapeutic markets, that qualify for BARDA awards and defined them as my treatment group. I further define my treatment variable as being in the treatment group after the introduction of the Pandemic and All-Hazards

Preparedness Act in December of 2006. My final sample has 1,680 year-market observations spanning 2001-2008.

4 Regressions

4.1. Competition and Learning Effects

To measure competition effects, my baseline specification is a panel probit model using the development panel data for projects in phase 1, 2 and 3 clinical trials. As a dependent variable, I use an indicator for whether the project was terminated on a given semester. Given the binary nature of the dependent variable, probit is an appropriate model to determine the significance of the effects of competition and technology learning. The regression model is

$$i(Termination)_{i,t} = \beta_0 + \beta_1(NUM.\ REG.)_{i,t} + \beta_2(NUM.\ IN\ DEVELOPMENT)_{i,t}$$
$$+ \sum(YEAR\ \&\ MARKET\ F.E.) + \sum_j \lambda_j\ (FIRM\ SIZE\ INTERACTIONS)$$

where $i(Termination)_{i,t}$ is the indicator on whether the project was terminated that semester, $(NUM.\ REG.)$ is the number of registered projects that compete in the same condition market, and $(NUM.\ IN\ DEVELOPMENT)_{i,t}$ is the number of projects in the same condition market that are in development during semester *t*. I also include stratified versions of these competition variables by competitor's firm size in alternative specifications.

Finally, $(YEAR\ \&\ MARKET\ F.E.)$ are the year and market fixed effect interactions, which account for therapeutic market differences and their variation by year.

In order to estimate the effect of technology learning by competitors' success I use the regression

$$i(Termination)_{i,t} = \beta_0 + \beta_1(NUM.\ REG.\ COMP.)_{i,t} + \beta_2(NUM.\ IN\ DEVELOPMENT\ COMP.)_{i,t}$$
$$+ \beta_3(NUM.\ REG.\ NOT\ COMP.)_{i,t} + \beta_4(NUM.\ IN\ DEVELOPMENT\ \ NOT\ COMP.)_{i,t}$$
$$+ \sum(YEAR\ \&\ MARKET\ F.E.) + \sum_j \lambda_j\ (FIRM\ SIZE\ INTERACTIONS)$$

where $(NUM.\ REG.COMP.)_{i,t}$ is the number of competing projects by condition that share the same target (technology) with registered status, $(NUM.IN\ DEVELOPMENT\ COMP.)_{i,t}$ is the number of competing projects with the same technology being developed during that semester, and the variables with β_3 and β_4 coefficients are respectively those numbers for non-competing projects.

Finally, to understand the effects of competition and their interaction with the phase of development for the competitors, I use the regression

$$i(Termination)_{i,t} = \beta_0 + \beta_1(NUM.\ I)_{i,t} + \beta_2(NUM.II)_{i,t} + \beta_3(NUM.III)_{i,t}$$

$$+ \sum(YEAR\ \&\ MARKET\ F.E.)$$

where β_1, β_2, and β_3 are the coefficients for the variables counting the number of competing projects (same condition) by phase 1, 2, and 3 respectively.

4.2. Public Funding

Analyzing the effect of public funding on success rates and strategic behavior presents the burden of dealing with self-selection and omitted variable bias. In particular, I am interested in controlling for the innate technological potential for each project. Since the QTDP, SBIR/STTR and BARDA fund projects with demonstrated potential, I would expect projects that received these grants to have a higher probability of success regardless of treatment assignment. The award process for each of these grants and contracts involves a grading system that could provide a measure for the potential of those projects that were submitted for consideration; however, the review results are confidential and not publicly available given the sensitivity of the information that firms share with the awarding institutions. One potential way to control for selection bias to a certain extent is to include some control variables based on the observable data that I have access to.

A set of variables that are possibly good controls for omitted variable bias are those that summarize the information submitted to the government agency by the firm when applying for a

grant. These variables will be correlated with grant status. For instance, firm size is a relevant control since most of these programs target projects owned by the small firms. Another obvious control is the therapeutic market of a project, since these grants target certain conditions. As discussed above, another potential source of bias is the correlation between innate project potential and grant status. Controlling for this unobservable is particularly difficult. I suggest below some variables that might be useful in controlling for innate project potential. Nevertheless, a key variable is missing from my data set. I do not have data on pre-clinical trial results and phase 1 clinical trial results. This data is very relevant in determining innate project potential (by definition these results aim to measure the potential of the project), and is observed by the government agency prior to awarding the grant in the case of the BARDA program, and partially observed by the government agency in the case of the QTDP and STTR/SBIR programs. This is a big limitation to my analysis. However, with the data that I have access to, I can aim to show that innate-project-potential-driven bias is relevant for this type of analysis by looking at how my results change with the incorporation of variables that account for this type of bias.

When running the linear model to analyze the effect of the QTDP, SBIR/STTR and BARDA, I include a series of controls that attempt to measure potential. In addition to year and therapeutic market controls, I include the following:

1. **Firm size:** With high correlation to both success rates and treatment assignment, this variable is highly relevant. All programs consider firm size (in terms of number of employees) before awarding a grant or a contract.
2. **Technology type:** Including variables such as mechanism and target technology can serve as a control for innovation and technological potential given the heterogeneity in success rates among these categories.
3. **Lipinski's rule:** This rule is used in the industry to measure the drug-likeness of a compound.

4. **Private sector partners**: This variable tells us whether a project is the result of collaboration with other private sector agents.

While these variables might not account for all the omitted variable bias, they can shed light on the direction of the bias and how it affects the estimates of the effects of each of these government programs.

4.3. Industry wide effects of the introduction of BARDA by a difference in differences approach

I use a difference in differences estimator for the effect of the introduction of the BARDA program on the number of new research projects in a year by therapeutic market as well as their respective success rates. The standard specification is:

$$New\ Projects_{it} = \beta_0 + \beta_1 Treat_{it} + \sum (YEAR\ F.E.) + \sum (MARKET\ F.E.)$$

where $Treat_{it}$ is an indicator for whether the observation is after the introduction of BARDA in December 2016 and the market qualifies for a BARDA contract.

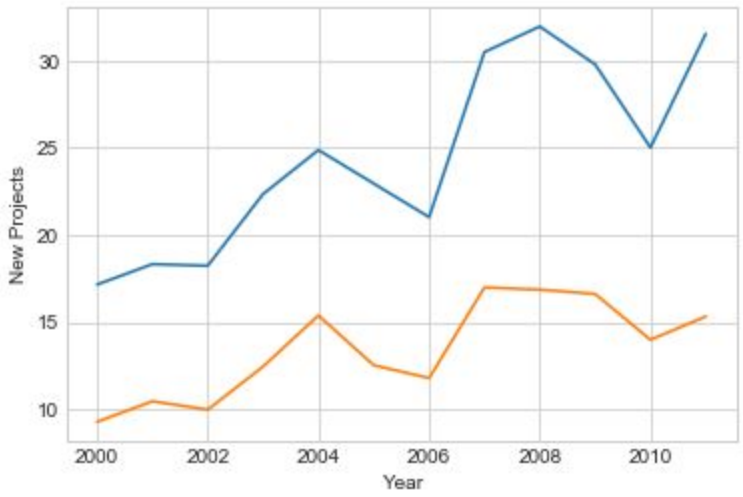
To test the parallel trends assumption, necessary to make this estimator consistent, I use the following regression:

$$New\ Projects_{it} = \beta_0 + \sum (BARDA * YEAR) + \sum (YEAR\ F.E.) + \sum (MARKET\ F.E.)$$

Where $\sum \beta_j\ (BARDA * YEAR)$ are the interaction terms of being in year $j \in \{2001 - 2008\}$ and being a qualifying BARDA therapeutic market, and forcing the 2006 coefficient to be 0 (equivalent to dropping this interaction term due to multicollinearity). In this case, we would expect the coefficients of the interaction terms for $j \in \{2001 - 2005\}$ to be non-significantly different from 0, if we expect parallel trends to be a valid assumption. Also, a simple observation of the time trends of the control and treatment groups (qualifying of BARDA) can give us confidence that this assumption is likely to hold, as shown in figure 5 below.

I use the same approach to measure the impact of the introduction of BARDA on the number of successful projects produced in year in BARDA qualifying industries.

Figure 5: time trends in number of new projects for BARDA-qualifying (blue) and non-BARDA-qualifying (orange) markets



5 Results and Discussion

5.1. Competition effects

The results from my econometric analysis suggest that the estimations by previous literature hold true for projects in all phases of the clinical trials development stage. Firm size is also a relevant factor in determining the probability of termination. Overall, the greater the firm size of the competitor, the higher the competition effect. I also find evidence that the magnitude of the effect of the presence of competition is dependent on the phase of development of the competitor's project.

For my first specification, we can observe competition effects in the probability of termination. In model one, my most simple specification, there is an effect on the probability of termination of a drug project in a given semester by the number of registered projects that were developed in the same therapeutic market, with a coefficient of 0.037 in the probit regression with a p-value less than 1%. The number of projects being developed that are competing in the same therapeutic

market also has, although to a lesser degree, a significant marginal effect on the probability of termination. In order to interpret these results we can look at the average marginal effect on the probability of termination. The marginal effect is 0.0019 for number of registrations and 0.0008 for number of developing projects based on the previous probit coefficients. In relative terms, an additional registration leads to an increase of 9% in the probability of termination, and an additional project in development leads to an increase of 4% for competing projects. However, considering that the mean number of competing projects being developed at a given time is 73.2 versus a mean of 15.42 competing projects registered, the absolute magnitude of the competition effect coming from the presence of competing firms has a bigger overall impact on the probability of termination for the average drug project.

Table 2: Competition effects, firm size and phase of development probit models

	(1)	(2)	(3)
	Terminated = 1		
	Main	Firm Size	Competition Phase
Number registered	0.037***	0.034***	
Number in development	0.017***		
Number in development small		0.014***	
Number in development medium		0.014***	
Number in development large		0.019***	
Originator size		-3.8e-5*	
Originator size squared		9.2e-9	
Number of competitors in Phase 1			-0.042**
Number of competitors in Phase 2			0.021*
Number of competitors in Phase 3			0.070***
Disease-Semester Fixed Effects	Yes	Yes	Yes

A probit regression model was used. The dependent variable is an indicator of whether the observed project was terminated in a given semester. Model (1) and (2) measure competition effects. Model (3) measures competition effects through the presence of competitors in the develoment stage by clinical trial phase. Number registered refers to the number of competing registrations with a government agency. Numbers in development refer to the number of firms competing in the same therapeutic market in that semester. Disease and semester fixed effects include interactions between therapeutic markets and semesters. ***, **, and * indicate significance at the 1%, 5%, and 10% levels, respectively.

An interpretation of this result is that presence of competition in the development stage is taken into account by the firm when deciding on whether to continue or terminate a project. The existence of competing projects in the development phase, even in the absence of news of success, can therefore be a relevant factor. Nevertheless the marginal effect of success news from competitors is still larger.

In my second model I stratify the competition variables (number of developing projects and number of registered projects) by the size of the competitors. The results suggest that firms weigh news of success and competition presence differently depending on the size of the competitor. In particular, the larger the competing developing firms are, the greater the probability of terminating a project before registration. Although the impact of small competitors seems to be similar to the impact of medium competitors, this might be related to the fact that medium firms and small firms, as defined in my analysis, are not that different in size. This is because the majority of the firms in the medium category are near the threshold that separates the two categories (refer to Figure 2). Using two size categories instead of three leads to similar results (see appendix C). Nevertheless, the impact of the presence of large competitors is significantly greater than the impact of smaller competitors, suggesting that firms are more intimidated by industry leaders. In order to control for the firm's own size I use the total number of projects in my data set owned by the firm. For model 2, I assume a quadratic functional form with respect to this variable since marginal effects might vary depending on the size of the firm. I include the results for the linear functional form in appendix C. As it would be expected, unconditional to the number of competing firms, smaller firms still have a higher probability of termination, hinting to the financial and technical burdens of the clinical trials stage. The coefficients for these size variables, however, are not jointly significant when using an F-test (p-value of 13%. Linear functional form is not significant either to the 90% confidence level). In my third model, which incorporates the competitor's stage of development, the higher the stage of development of a competitor, the higher the impact on the probability of termination. Particularly, comparing the impact between a phase 1 and a phase 3 competitor's presence, there is a clear difference that is statistically significant (to the 95% level). A concern for these results

is that even though I complemented my data with clinical trial stages using the NIH's registry, I am still missing the complete life-cycle of several pharmaceutical projects. Running this regression with a data set with more entries on clinical stages would not only improve the significance of these results but would also allow the researcher to understand the interactions with size and other market indicators.

5.2. Learning from technological developments

The following regressions pertain to my second specification, where I try to understand the effect of learning technology effects when a competitor is successful and whether this effect dominates over the competition effect. The results in table 2 suggest that learning from competitors' successes dominates over competition effects, which is consistent with Krieger's results (2017). By looking into the number of technologically similar projects in development versus the number of technologically similar projects registered, we can see when each of the effects dominates; the learning effect dominates when considering competition successes and the competition effect dominates when looking at the presence of competitors.

In the first model from Table 3, we can see the baseline specification for estimating technology learning effects from competitors' successes. When looking at the number of competing projects (in the same therapeutic market) developing a similar technology, we see that the competition effect seems to dominate since the positive coefficient of 0.010 in the probit regression is highly significant and implies that the probability of termination is still higher with an additional unit in the number of such competing projects. However, there seems to still be an effect of learning reinforcement with the presence of other firms doing research in the same technology since, compared to the specifications from section 5.1. relating to competition without accounting for similar technologies, the coefficient for the number of development projects is smaller when they overlap in technology (0.01 vs 0.017). Hence, I find evidence that suggests that even before there are actual signs of success from competitors (i.e., competing project registrations), the presence of other firms doing research on a similar technology leads firms to positively update their

expectations on whether the drug will be approved or not, even though overall, without a clear sign of success from competitors, the competition effects still dominate at this stage.

Table 3: Competition fixed effects vs. learning effects probit models

	(1)	(2)	(3)
	Terminated = 1		
	Main	Firm Size	Not competing
№ registered similar tech. competing	-0.032***		-0.028***
№ developing similar tech. competing	0.010***		0.009***
№ developing similar tech. not competing			0.006***
№ registered similar tech. not competing			-0.012***
№ registered similar tech. by small firm		-0.063*	
№ registered similar tech. by medium firm		-0.049***	
№ registered similar tech. by large firm		-0.032***	
№ developing similar tech. by small firm		0.032***	
№ developing similar tech. by medium firm		0.008**	
№ developing similar tech. by large firm		0.005**	
Disease-Semester Fixed Effects	Yes	Yes	Yes

A probit regression model was used. The dependent variable is an indicator of whether the observed project was terminated in a given semester. Model (1), (2) and (3) measure learning effects. Number registered refers to the number of competing registrations within the FDA. Numbers in development refer to the number of firms in the same therapeutic market in that semester. All size interactions are for competing projects. Not competing status refers to projects in a different therapeutic market. Disease and semester fixed effects include interactions between therapeutic markets and semesters. ***, **, and * indicate significance at the 1%, 5%, and 10% levels, respectively.

When I consider instead the number of registered projects from competing firms in model 1, it seems like the technology learning effects overcome the competition effects. Looking at the number of registered competing projects with an overlap in technology, we can see an overall negative impact on the probability of termination for a given project. With a coefficient of -0.032, this result contrasts with the results from Table 2 where technology overlap was not considered (where the number of competing registrations had a coefficient between 0.034 and 0.037). An interpretation to these results is that not only do learning effects dominate competition effects, but the magnitude of such effects is significantly larger. This sheds light on an important factor when determining strategic decisions about whether to terminate a project or not. Even though the prospect of competition once a drug is registered are relevant in influencing

a firm's decision, firms could weigh information pertaining to the probability of approval by the FDA and registration with more importance. This can be viewed as a rational decision since registration status is a precondition to competition in the consumer market and, given the low probability of registration in the first place and the level of investment that a pharmaceutical research project represents, being able to access the market could be weighed more heavily. However an alternative explanation is that the technology that got approved by the FDA results in better outcomes at the clinical trials stage for the different drugs that rely on it since it works (as proven by the registration). This also increases the probability of continuing development for those drugs.

In model 2 I examine the dynamics of model 1 but stratifying the competition variables by the competitor's firm size. When looking at the number of registered competing projects with an overlap on technology by firm size, we can see how the effect is greater when the firm that obtained the registration is small or medium. Hence, similar to our results of interactions with firm size in section 5.1., firms are 'intimidated' even more by the success of their large competitors relative to smaller competing firms. Even though there are issues with significance for small firm registrations with overlapping technologies (only 10% significance level), we can appreciate this pattern for medium and large firms. Since the number of small firms that attain registration status is very low, when interacting with competition and overlapping technology we are left with few observations and this leads to a low significance level. When considering the number of developing competing projects with a technology overlap by size, I find an intriguing pattern: the greater the competitor, the lower the probability of being terminated, and the smaller the competitor, the higher the probability of terminating the project. This might be the result of another interesting dynamic with learning effects. When a large competitor is investigating a similar technology, it might signal other firms the potential that the technology might have, especially when accompanied with more heavy investment. In addition, the greater access to resources by a large firm also implies more precise results at the clinical trial stage, which make positive clinical trial results by large firms have a greater learning effect on competitors. It would be interesting to analyze this dynamic by including variables that proxy the cost of development

of the project to see how investment by competitors in overlapping technology projects signals to other firms the potential that the technology might have.

Finally, for model 3, I compare the learning effects from competing projects versus non-competing projects. The absolute magnitude is smaller for both cases, number of registrations and number of developing projects, when considering non-competing firms, but signs are conserved. The positive sign in the number of non-competing projects being developed (0.006) suggests that the competition effects still have an influence even when talking about distinct therapeutic markets since firms might enter other markets with the same drug project in the future. The average number of competing projects with a similar technology is 3.4, while the average number of non-competing projects with a similar technology is 1.9. This pattern could suggest to firms that non-competing projects are potential competitors given the similarities in technology. However, the lower magnitude in the regression estimates relative to competing projects suggests that the threat from competition is lower. In addition, the effect from the number of registrations for non-competing technologically overlapping projects on the probability of termination is also of lesser magnitude (i.e., it does not increase the probability of survival by as much as competing projects). This might hint that learning from projects in the same therapeutic market is more relevant, especially since the FDA approves projects based on the condition being treated, so a drug that was approved in one therapeutic market can still be rejected for a different market. Nevertheless, there is still a learning effect that overcomes any competition effects that might be present.

5.3 Success rates and government programs

I present here my results for the regressions discussed in section 4.2. In table 3, we can observe the results from running a linear model with various controls on the probability of success of a given project given that they received a SBIR, QTDP or a BARDA award. In model 1, having no controls, we observe that BARDA supported projects have a very high probability of being approved with an increment of 0.1831 in the probability of approval, while QTDP funded projects also have a higher probability of approval than non-grant funded projects with a

coefficient of 0.0504. However, SBIR projects have a lower probability of approval than non-grant-supported projects with a negative coefficient of -0.0436. SBIR's negative coefficient might be due to firm size effects. As discussed in an earlier section, the SBIR/STTR program funded only projects whose originators are small firms with less than 500 employees. In addition, in contrast with QTDP projects, none of the SBIR projects were acquired by a larger firm at a later stage. Therefore, these projects tend to have less access to resources than projects funded by other grants. Furthermore, SBIR might select for relatively more risky projects than QTDP and BARDA in terms of technology based on their project requirements.

Table 4: Success rates by grant status

	(1)	(2)	(3)	(4)	(5)
	Success = 1				
STTR/SBIR	-0.04361***	-0.04205***	-0.04799***	-0.04018***	-0.08079***
QTDP	0.05041***	0.03818***	0.01567*	0.01412*	-0.03289***
BARDA	0.18312***	0.15088***	0.13594***	0.11863***	0.09817**
Year and therapeutic class controls	No	Yes	Yes	Yes	Yes
Firm size controls	No	Yes	Yes	Yes	Yes
Lipinski's rule control	No	No	Yes	Yes	Yes
Technology type controls	No	No	No	Yes	Yes
Private sector partners controls	No	No	No	No	Yes

STTR/SBIR, QTDP and BARDA are indicators for whether that grant was received by the project. Firm size controls use my size metric as defined before, assuming a quadratic functional form. Results are not statistically different from using a linear functional form. Lipinski's rule control is an indicator for whether the compound satisfies the rule. Technology type controls include target and mechanism. Private sector partner is an indicator for whether the project is the result of a collaboration between 2 or more firms. ***, **, and * indicate significance at the 1%, 5%, and 10% levels, respectively.

After incorporating size and therapeutic market controls, the coefficients for both BARDA and QTDP decrease, while SBIRs coefficient increases slightly. This result could be expected given our previous discussion where SBIR projects tend to be owned by smaller firms relative to QTDP and BARDA supported projects. Models 3-5 include additional variables that account for innate project potential. It is interesting to note that after accounting for firm size, adding additional controls for innate potential lead to changes in the coefficients for QTDP and BARDA

in the same direction and in mostly similar magnitudes. This suggests that there is a significant positive bias when measuring the effect of these two programs on success rates. Given the selectivity of the application process of these government interventions, it is not surprising that these programs tend to attract projects that have above average expectations of success regardless of the effect of these programs. Nevertheless, that does not seem to be the case for the SBIR program, where accounting for technology type controls (which include the drug's target and mechanism of action) lead to an increase in the coefficient. This could suggest that this program might fund projects that incorporate more risky technologies in terms of approvals. Model 5 incorporates a variable that accounts for private partnerships as well as other private sources of external funding. An interesting result is that the QTDP coefficient becomes negative after including this variable. The figures in appendix B show that relative to SBIR, the QTDP projects have partner firms of larger size.

I do not believe that the innate potential variables that I incorporate into my analysis control for all of the omitted variable bias, since we do not observe the results from the preclinical trial stage (or the phase 1 clinical results if appropriate), which are used by the US government in determining the awardees of these programs. Nevertheless, the result that BARDA has a much larger effect than the other two programs is consistent across all regressions and could be the result of the structure of these contracts. While the QTDP and SBIR programs consist of monetary awards during the preclinical trials phase, BARDA usually awards contracts to projects that have some phase 1 clinical trials results, which naturally leads to a selection of projects with higher potential. In addition, the financial and technical resources that a BARDA contract offers are far superior to the grants and tax incentives given by the QTDP and SBIR programs. Therefore, given the limitations with my data, it is not possible to disentangle the effect of the structure of this program on success rates from the highly possible positive bias on success rates driven by the project's innate potential as an omitted variable.

5.3 Market-specific incentives: The effect of the BARDA program in the production of new projects

While looking at project-specific success rates comes with big identification issues as discussed in the previous section, analyzing the effect of the BARDA program on the number of new projects generated by year leads to more promising results. For this section, I take advantage of a natural experiment: the creation of the BARDA agency, along with the introduction of its contracts in December of 2006. Given the broad categories of therapeutic markets that are eligible for BARDA contracts, the "treatment" group for this analysis includes a diverse portfolio of therapeutic markets, from common conditions such as cancer, to under-researched infections such as the Zika virus.

Table 5: Difference in Difference estimator for BARDA industry effects

	(1)	(2)	(3)	(4)
	№ of new projects		№ of successful projects	
2001*BARDA	-1.368		-0.000	
2002*BARDA	-0.977		-0.193	
2003*BARDA	0.661		0.237	
2004*BARDA	0.253		-0.076	
2005*BARDA	1.185		-0.191	
2006*BARDA	0.000		0.000	
2007*BARDA	4.268***		-0.707**	
2008*BARDA	5.854***		-0.718**	
BARDA*(Post 2006)		5.102***		-0.675***
Disease-Year Fixed Effects	Yes	Yes	Yes	Yes

BARDA is an indicator for whether the therapeutic market qualifies for BARDA contracts. Models 2 and 4 are restricted to 2005, 2006, 2007, and 2008. Restricting to 2006 and 2007 leads to similar results. ***, **, and * indicate significance at the 1%, 5%, and 10% levels, respectively.

Table 5 summarizes the results of the difference in difference estimation. Model 1 tests the parallel trends assumption by showing the coefficients of the year-BARDA eligibility interaction variables before and after the intervention, where the dependent variable is the number of new projects generated by year. It is clear from these results that the parallel trends assumption is reasonable in this context: being in the treatment group before 2006 does not lead to significant

differences in time trends. Furthermore, these interaction variables grow significantly in magnitude post 2006, when the BARDA agency was created and contracting started. A visual examination of figure 5 in section 4.3 shows that a parallel trend assumption is a fair one. Hence, as model 2 shows, there seems to be a significant positive effect in the number of projects started after 2006 in those therapeutic markets that qualify for BARDA, with 5.1 additional projects created on average per treated industry in 2007 in response to this program with 99% confidence. This is an additional 20% increase in the production of new projects relative to 2006 levels for the average therapeutic market.

It is relevant to understand the outcome of those projects created in response to BARDA. In order to do so, I use a difference in difference estimator in a similar way to estimate the effect on the number of eventually successful projects created by year. Model 3 shows that the parallel trends assumption seems to hold, where pre-2006 coefficients seem to be guided by random noise. A visual inspection of the parallel trends (Appendix A) shows that the parallel trends are not as clear as in the case of new project counts, so this result is not as robust as for the regression in model 2. Nevertheless, this estimator leads to an interesting result: there is a negative effect in the number of eventually successful projects created during 2007 in the treatment group.

Both results shed light on an interesting dynamic. It seems like the existence of the BARDA contracts incentivizes firms to start pre-clinical trials for projects in therapeutic markets that qualify for support. Congress initially authorized 1.07 billion dollars in funding for BARDA for the 2007 fiscal year under the Pandemic and All Hazards Preparedness Act of 2006. According to research done by Chakma et al (2014), the United States industry's investment in 2007 in R&D activities was 83 billion dollars in total. According to the Kaiser Family Foundation, a third of R&D costs go into the clinical trials stage (2019). A simple calculation using the previous amounts suggests that funding at the clinical trials stage increased by approximately 5% that year due to BARDA. Since this funding was not available for all therapeutic markets, this shock was possibly even greater than 5% for those markets that qualified for BARDA.

Nevertheless, a 20% increment in research activities attributed to the introduction of BARDA in 2006 might seem like a disproportionate reaction. One should consider, however, that the increase in research activity was at the pre-clinical trial stage, which precedes the application for a BARDA contract (firms need to have phase 1 clinical trial data in order to apply). Pre-clinical trial studies are disproportionately cheaper relative to other stages of the development process, so firms might be incentivized to start pre-clinical trials for projects that qualify for BARDA contracts and use those results to weigh whether or not to continue investing in those projects. Spillover effects from such research activities might further contribute to this increase in research activities at early stages as seen in the existing literature (Furman et. al., 2016). This positive effect in early-stage research activities does not necessarily imply that the higher research activity levels are sustained during all stages of the development process. In fact, as seen in the results from model 4, there was no positive impact at all stages of the development process.

Looking into the success rates of these projects allows us to better understand the actual impact of this policy. The results from model 3 are intriguing: even though there were more products in development during 2007 due to BARDA, there were fewer successes in terms of product approval, 0.7 less projects on average per industry with p value of 0.01. This dynamic could have several explanations. One potential reason for this pattern is that the policy incentivized firms to develop projects with higher inherent risk but with greater potential for being groundbreaking innovations. Since BARDA selects projects based on potential to increase the national bio-defense stockpile, projects that address issues in therapeutic markets that have yet to be solved have a competitive advantage in the application process. At the same time, firms have a constraint on resources, so starting trials on more risky projects can lead to a reduction in research activities for less-risky projects due to the shift in the allocation of funds. An alternative explanation could be that the availability of these funds incentivizes firms to start trials on projects that otherwise would not be a priority for the firm, and after realizing that their project will not be funded by BARDA, those projects are terminated early. In addition, starting

these trials could take funds away from other projects that would be successful otherwise, leading to an overall decrease in the number of successful projects that started that year.

A potential issue with the definition of the success variable is that a project's success does not depend solely on the year when they started, and there could be other temporal trends post-2006 that affect the treatment group differently from the control group, leading to diverging success outcomes not directly related to the BARDA program. This is a limitation of the difference in difference approach used, making the results from models 3 and 4 less robust. This is not a concern for models 1 and 2 since the outcome variable is measured on the same year as the start year of the project.

6 Conclusion

I find further evidence to validate the results from Rao (2015) and Krieger (2017) regarding the negative impact on probability of a drug project's continuation from competition effects and the positive impact on that probability from learning effects when competing drug projects that are based on a similar technology are successful. Firm size is positively related with the magnitude of the competition effect, and it is also positively related with the learning effects from the presence of other technologically similar competing projects. In addition, I find that learning effects are present when a firm observes other competitors develop technologically similar projects, but these effects dominate over competition effects only when there is positive news relating to registration decisions by the FDA, where the viability of the technology is proved.

For future research, improving the quality of the information pertaining clinical trial phases on a given semester could allow us to observe the interactions between the competition's phase of development and firm size with statistical significance. This could be done by either using other sources of clinical trial information or considering the data from the World Health Organization's International Clinical Trials Registry Platform which includes data from other global agencies. Also, increasing the subset of drug-indication entries that reached the clinical trial stage by considering other indications in addition to the 20 I used and matching it with

clinical trial data could allow us to use information pertaining to the number of facilities utilized in a given experiment to create a proxy for the cost of the development process of a drug project, which can allow us to observe other relevant interactions and control for potential biases.

In estimating the effects of public-private collaborations, I find that innate project potential bias is a significant concern when looking at success rates at the project level. However, by exploiting the introduction of the BARDA program in 2006 as a natural experiment by using a difference in difference approach, I was able to estimate the initial overall effect in the industry from this program. BARDA incentivizes firms to produce more projects in those therapeutic markets that are targeted by the program which can be seen as a successful outcome. However, the introduction of BARDA had a negative effect on the number of successful projects produced. This negative effect does not necessarily imply a policy failure since BARDA funds projects with greater innovative potential, which may encourage firms to invest in more risky projects that have an innately lower probability of success. Further research pertaining the mechanisms of this dynamic could be fruitful in clarifying these observations.

References:

Adams, C. P. and Brantner, V. V. (2010), Spending on new drug development. Health Econ., 19: 130-141. doi:10.1002/hec.1454

Bere, Nathalie. "How Are Medicines Evaluated at the EMA." European Medicines Agency, 2015, www.ema.europa.eu/en/documents/presentation/presentation-how-are-medicines-evaluated-ema-nathalie-bere_en.pdf.

Chakma, Justin, et al. "Asia's ascent—global trends in biomedical R&D expenditures." New England Journal of Medicine 370.1 (2014): 3-6.

Chin, Jane. "Do Pharmaceutical Companies Seek Approval Outside The US If The FDA Is Slow?" Forbes, Forbes Magazine, 10 Nov. 2017, www.forbes.com/sites/quora/2017/11/10/do-pharmaceutical-companies-seek-approval-outside-the-us-if-the-fda-is-slow/#2d371742356b.

Cockburn, Iain, and Rebecca Henderson. "Exploring inertia: Complementarities and firm effects in pharmaceutical research." Mimeo, MIT April (1996).

Cockburn, Iain, and Rebecca Henderson. Public-private interaction and the productivity of pharmaceutical research. No. w6018. National Bureau of Economic Research, 1997.

Cunningham, Colleen, Florian Ederer, and Song Ma. "Killer acquisitions." Working Paper (2017)

Dorsey ER, de Roulet J, Thompson JP, et al. Funding of US Biomedical Research, 2003-2008. JAMA. 2010;303(2):137–143. doi:10.1001/jama.2009.1987

Dorsey ER, de Roulet J, Thompson JP, et al. Funding of US Biomedical Research, 2003-2008. JAMA. 2010;303(2):137–143. doi:10.1001/jama.2009.1987

Franco, Crystal. "Billions for Biodefense: Federal Agency Biodefense Funding, FY2008-FY2009." Biosecurity and Bioterrorism: Biodefense Strategy, Practice, and Science, vol. 6, no. 2, 2008, pp. 131–146., doi:10.1089/bsp.2008.0025.

Furman, Jeffrey L., et al. Public & private spillovers, location and the productivity of pharmaceutical research. No. w12509. National Bureau of Economic Research, 2006.

Giffin, Robert, Sally Robinson, and Theresa Wizemann. Breakthrough business models: Drug development for rare and neglected diseases and individualized therapies: Workshop summary. National Academies Press, 2009.

Krieger, Joshua L. Trials and Terminations: Learning from Competitors' R&D Failures. Harvard Business School, 2017.

Marietta, Cynthia S. "Qualifying Therapeutic Discovery Project Tax Credit Program Will Give Economic Boost to Eligible Biotech Firms " UH Law, University of Houston, 2010, www.law.uh.edu/healthlaw/perspectives/2010/(CM)%20QTDP.pdf.

Pierre Azoulay, Joshua S Graff Zivin, Danielle Li, Bhaven N Sampat, Public R&D Investments and Private-sector Patenting: Evidence from NIH Funding Rules, The Review of Economic Studies, Volume 86, Issue 1, January 2019, Pages 117–152, https://doi.org/10.1093/restud/rdy034

Rao, Anita. (2015). Entry and Investment Decisions in the Pharmaceutical Industry. SSRN Electronic Journal. 10.2139/ssrn.2652755.

Sertkaya, Aylin, et al. "Examination of Clinical Trial Costs and Barriers for Drug Development." ASPE, Assistant Secretary for Planning and Evaluation, 16 June 2016, aspe.hhs.gov/report/examination-clinical-trial-costs-and-barriers-drug-development

Thiers, Fabio Albuquerque. The globalization of clinical drug development. Diss. Massachusetts Institute of Technology, 2006.

Wynacht, Peter. "Recapping Section 48D (qualifying therapeutic discovery project credit)− Will it be extended?." Journal of Commercial Biotechnology 17.3 (2011): 272-275.

Yildirim, Oktay et al. "Opportunities and Challenges for Drug Development: Public-Private Partnerships, Adaptive Designs and Big Data." Frontiers in pharmacology vol. 7 461. 6 Dec. 2016, doi:10.3389/fphar.2016.00461

Yildirim, Oktay et al. "Opportunities and Challenges for Drug Development: Public-Private Partnerships, Adaptive Designs and Big Data" Frontiers in pharmacology vol. 7 461. 6 Dec. 2016, doi:10.3389/fphar.2016.00461

"A Third Of Drug Development Costs Comes From Clinical Trials. Can Pharma Make Them Faster And Cheaper?" Kaiser Health News, Kaiser Permanente, 30 Jan. 2019, khn.org/morning-breakout/a-third-of-drug-development-costs-comes-from-clinical-trials-can-pharma-make-them-faster-and-cheaper/.

"FDA Acceptance of Foreign Clinical Studies Not Conducted Under an IND Frequently Asked Questions" FDA, U.S. Department of Health and Human Services, 2012, www.fda.gov/downloads/regulatoryinformation/guidances/ucm294729.pdf.

"Foreign Clinical Studies Not Conducted Under an Investigational New Drug Application." FDA, 2008, www.regulations.gov/document?D=FDA-2004-N-0061-0002&oldLink=false.

"International Arrangements - Mutual Recognition Agreement (MRA)." FDA, Office of the Commissioner, 2019, www.fda.gov/internationalprograms/agreements/ucm598735.htm.

"Office of Biomedical Advanced Research and Development Authority (BARDA) Broad Agency Announcement (BAA)." Biomedical Advanced Research and Development Authority, Department of Health and Human Services, 2019, www.fbo.gov/index?s=opportunity&mode=form&id=68a2a601e291d1329140ca95f281b7d3&tab=core&_cview=0.

"Qualifying Therapeutic Discovery Project Credit." Hart Health Strategies, 2011, primaryimmune.org/wp-content/uploads/2011/10/X19-QualifyingTherapeuticDiscoveryProjectUPDATED063111.pdf.

"Qualifying Therapeutic Discovery Project Credits and Grants." IRS, 1 Nov. 2010, web.archive.org/web/20110704021723/http://www.irs.gov/businesses/small/article/0,,id=228690,00.html.

"Top 10 Pharmaceutical Markets Worldwide, 2017." IQVIA, 2017, www.iqvia.com/-/media/iqvia/pdfs/canada-location-site/top10worldwidesales_en_17.pdf?la=en&hash=C1D59CB0CB2B060CF458F14CF5390D96F3B28238.

"U.S. Investments in Medical and Health Research and Development 2013 - 2016." Research America, The Doris Duke Charitable Foundation , 2017, www.researchamerica.org/sites/default/files/RA-2017_InvestmentReport.pdf.

"Worldwide Pharmaceutical Company R&D Expenditure by Country." ABPI, 2016, www.abpi.org.uk/facts-and-figures/science-and-innovation/worldwide-pharmaceutical-company-rd-expenditure-by-country/.

Fiscal Year 2018 Budget-in-Brief, Public Health and Social Services Emergency Fund." Department of Health and Human Services, 2018, www.phe.gov/about/ofpa/Documents/bib-2018.pdf.

Institute of Medicine (US) Forum on Drug Discovery, Development, and Translation. Breakthrough Business Models: Drug Development for Rare and Neglected Diseases and Individualized Therapies: Workshop Summary. Washington (DC): National Academies Press (US); 2009. 2, Current Model for Financing Drug Development: From Concept Through Approval. Available from: https://www.ncbi.nlm.nih.gov/books/NBK50972/

National Institutes of Health, "ClinicalTrials.gov." United States, 2019

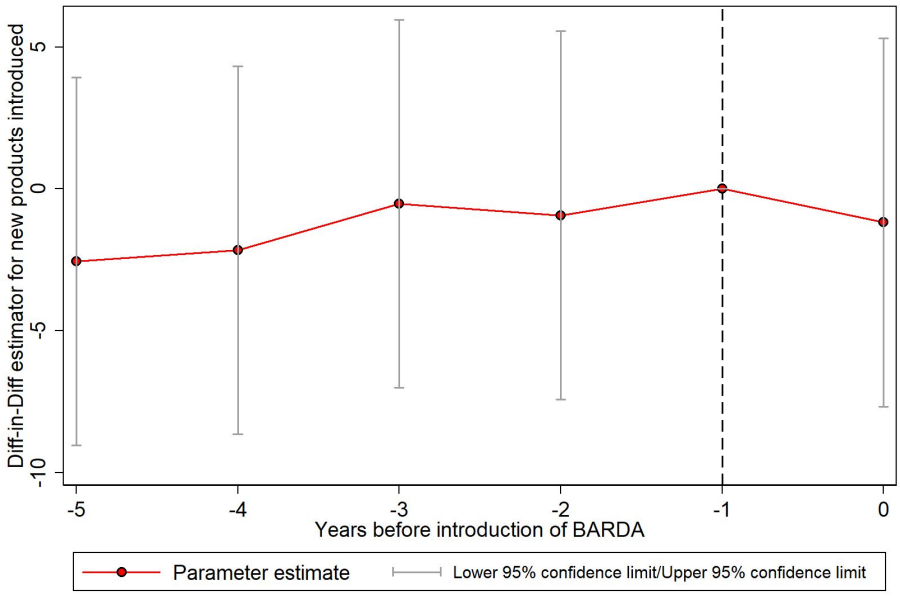
Office of the Commissioner. "The Drug Development Process." US Food and Drug Administration, Center for Biologics Evaluation and Research, 2018, www.fda.gov/ForPatients/Approvals/Drugs/ucm405622.htm.

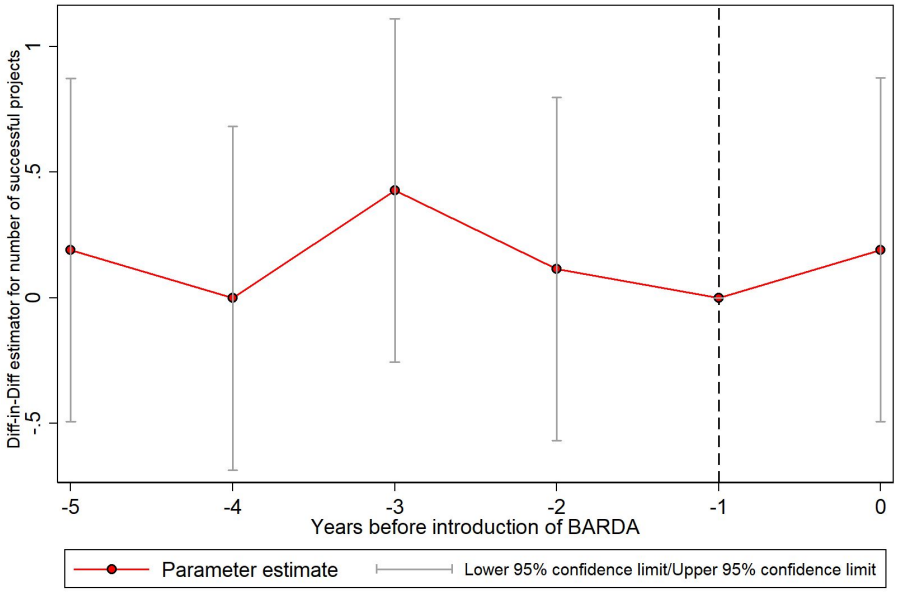
Pharma Intelligence, "Pharmaprojects" United States, 2017.

Qualifying Therapeutic Discovery Project Credits and Grants." Internal Revenue Service, U.S. Treasury, 2010, https://web.archive.org/web/20110704021723/http://www.irs.gov/businesses/small/article/0,,id=228690,00.html

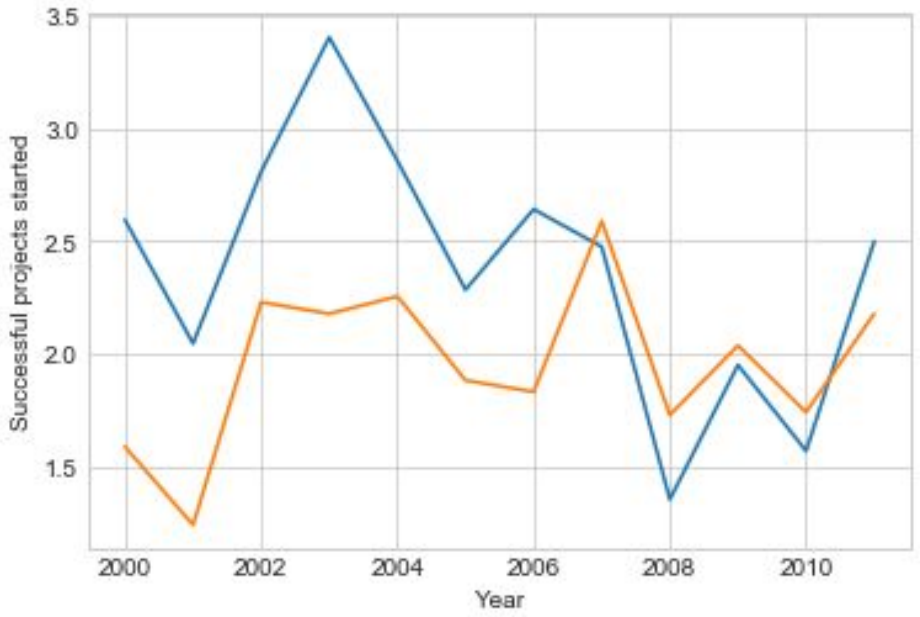
World Health Organization. The world medicines situation. No. WHO/EDM/PAR/2004.5. Geneva: World Health Organization, 2004.

Appendix A: Parallel trends check for the difference in differences estimator

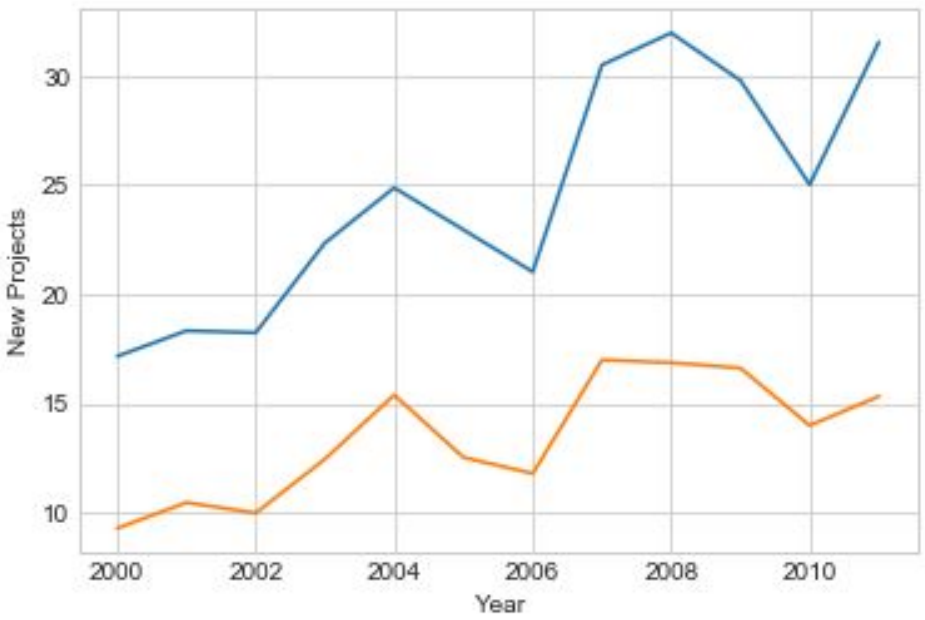




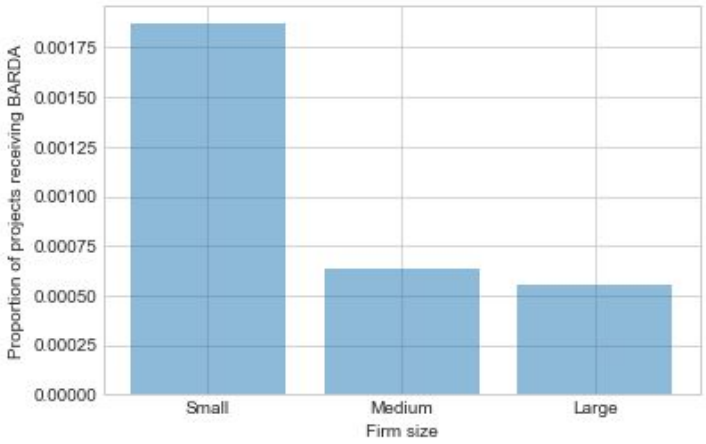
Time trends in average number of successful projects started for BARDA-qualifying (blue) and non-BARDA-qualifying (orange) markets

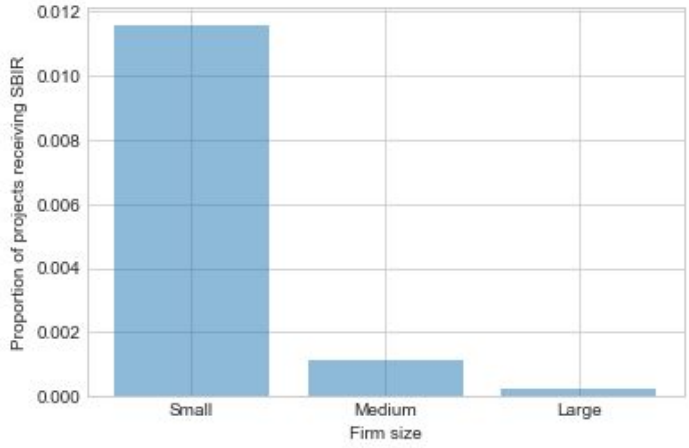


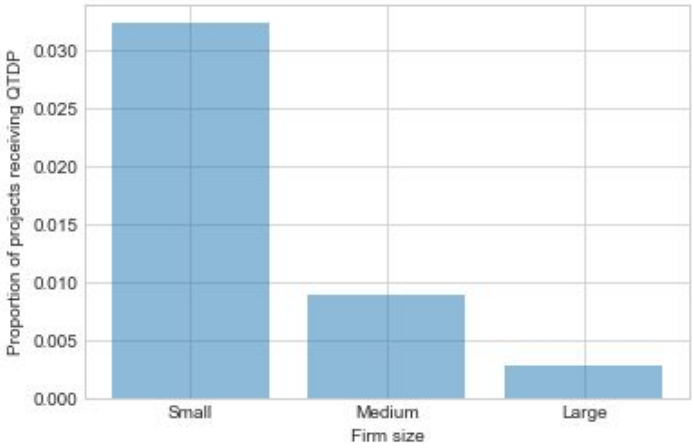
Time trends in number of new projects for BARDA-qualifying (blue) and non-BARDA-qualifying (orange) markets



Appendix B: Partner and originator firm size by grant status







Appendix C

	(1)	(2)
	Terminated = 1	
	Firm Size	Firm Size
Number registered	0.034***	0.034***
Number in development		
Number in development small	0.014***	
Number in development medium	0.014***	
Number in development large	0.019***	
Originator size	-8.15e-6	-3.8e-5*
Originator size squared		9.2e-9
Number in development bottom 66%		0.014***
Number in development top 33%		0.019***
Disease-Semester Fixed Effects	Yes	Yes

A probit regression model was used. The dependent variable is an indicator of whether the observed project was terminated in a given semester. Model (1) and (2) measure competition effects. Number registered refers to the number of competing registrations with a government agency. Numbers in development refer to the number of firms competing in the same therapeutic market in that semester. Small, medium and size are as defined in section 3.5. Number in development bottom 66% refers to firms with a size below the 66th percentile, while number in development top 33% refers to firms with a size above the 66th percentile. Disease and semester fixed effects include interactions between therapeutic markets and semesters. ***, **, and * indicate significance at the 1%, 5%, and 10% levels, respectively.