Emergent Forces in Health Care Management: The Role of Patients, Foundations & Digital Technology in Shaping New Product Development

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The undersigned, appointed by the Committee for the PhD in Health Policy have examined a dissertation entitled

Emergent Forces in Health Care Management: The Role of Patient Foundations and Digital Technology in Shaping New Product Development

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Emergent Forces in Health Care Management: The Role of Patient Foundations and Digital Technology in Shaping New Product Development

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Emergent Forces in Health Care Management: The Role of Patient Foundations and Digital Technology in Shaping New Product Development

Abstract

This dissertation investigates the role of emerging, external forces in shaping medical product development. Drawing on concepts from the technology innovation, nonmarket strategy, and health policy literatures, I evaluate 1) the role of a novel type of nonprofit: the patient-led, research-focused rare disease foundation, and 2) the growing use of digital health technologies in clinical research. The findings provide relevant, actionable implications for stakeholders interested in improving and accelerating the therapeutic development process, including patients, biopharmaceutical firm leaders, foundation managers, and regulatory policymakers.

In chapter 1, I propose a conceptual framework to explain how research-focused, patient-led rare disease foundations (RDFs) lower the risk of therapeutic development for industry firms in small, otherwise unattractive, markets by proactively engaging in research-complementary activities. First, I assemble a new dataset to describe and categorize the strategic activities pursued by RDFs. Then, empirically, I show that when an RDF adopts an *active* strategy—characterized by generation of novel data, creation of research tools, and establishment of collaborations across stakeholders—new clinical trial activity in the disease increases at a faster rate than when an RDF takes a *passive*, grant funding only approach, which has historically been typical of nonprofit foundations. I supplement this finding with a novel, quantitative case study of one RDF's successful strategy to engage firms in product development.

In chapter 2, I analyze partnerships between biopharmaceutical firms and RDFs in the development of novel rare disease drugs. I use a retrospective cohort design to compare average clinical development durations for approved, new molecular entity, orphan drugs that were developed with firm-RDF collaboration to similar drugs that were developed by firms-only (without RDF participation). I find that firm-RDF collaboration drugs spent on average 2.6 fewer years in clinical development than firm-only drugs (5.4 vs. 8.0 years, $p<0.01$). Notably, firm-RDF collaboration drugs rarely spent longer than the industry average in clinical development (7.5 years) whereas this was quite common for firm-only drugs. These findings suggest that such collaborations are nearly eliminating the "long tail" of development programs with protracted timelines. The research-complementary activities RDFs undertake may help firms avoid obstacles in clinical trial execution that typically plague rare diseases, such as challenges with patient recruitment, site identification, and endpoint selection.

In chapter 3 (with Ariel D. Stern), we analyze 20 years of clinical trial records to quantify growth in the use of digital health technologies (DHTs) over the most recent two decades (32% CAGR from 2000-2019). Noting lower technology adoption among trials sponsored by biopharmaceutical firms compared with non-biopharma organizations (e.g., academic medical centers, government entities), we compare DHT usage by sponsor type. We find clear evidence that when biopharma sponsored trials do use DHTs, those trials are more likely to be designated for regulatory review and study therapeutically addressable diseases rather than behavioral conditions, which is consistent with biopharma firms' pursuit of product development. Further, biopharma sponsors are more likely to use conventional sensor-enabled hardware (e.g., Holter monitors) rather than newer, software-enabled DHTs that lack a regulatory precedent (e.g. social media, mHealth apps). Recognition of these differences in DHT use by sponsor type could help regulators issue

guidance that encourages appropriate DHT adoption in product development trials where biopharma firms may be hesitant given the regulatory risk.

In summary, this dissertation provides evidence that external forces are altering traditional therapeutic development paradigms and sheds light on mechanisms driving these changes. Patient-led research foundations appear to be increasing clinical activity in rare diseases by changing incentives for product developers. To maximize their impact, RDF managers should invest in research-complementary activities rather than deploying resources only through traditional grant funding strategies. Accordingly, biopharma firms should seek partnerships with RDFs that are pursuing these activities to lower the risks associated with developing new therapies for rare diseases and help avoid costly delays in clinical development. Additionally, the rapidly growing use of digital health technologies has the potential to transform the conduct of clinical research. To further encourage appropriate technology adoption among biopharma firms sponsoring trials, regulators could consider establishing DHT best practices specific to the product development context.

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To my daughter Isabelle,

May you also find meaning in the pursuit of knowledge

Chapter 1 The Emerging Role of Research-focused Rare Disease Foundations in Therapeutic Development

Abstract

Several innovation incentives for rare disease product development exist, yet more than 90% of the 7,000 identified conditions have no treatment options. Over the last two decades, a novel type of nonprofit – the patient-led, research-focused rare disease foundation (RDF) – has emerged in many of these small, underserved markets with a singular goal to accelerate progress toward a cure. However, the collective role of these organizations in shaping product development for otherwise unattractive markets has been largely overlooked by the literature. In this paper, I assemble a new dataset to provide clarity around the role of RDFs and propose a conceptual framework to explain how RDFs lower the risk of therapeutic development for industry firms by proactively engaging in activities that build a research infrastructure within the disease. Empirically, I show that when an RDF adopts an active strategy characterized by generation of data, creation of research tools, and establishment of collaborations across stakeholders, new clinical trial activity in the disease increases at a faster rate than when an RDF takes a passive, grant funding approach. I supplement this finding with a novel quantitative case study describing one RDF's successful strategy to engage industry firms. These findings have implications for managers of both nonprofit foundations as they urgently pursue cure-seeking missions and biopharmaceutical firms as they decide which diseases merit investment.

1.1 Introduction

New product development decisions require firms to weigh development costs against expected revenue. Within biopharmaceutical innovation, this is a particularly complex decision due to high upfront capital requirements, substantial regulatory risk, and scientific uncertainty (Scott-Morton and Kyle 2011; DiMasi et al. 2016). Smaller markets, such as rare diseases that affect fewer than 200,000 patients, present challenges on both sides of the investment tradeoff, rendering these diseases relatively unattractive investment opportunities for drug development firms in absence of incentives (Acemoglu and Linn, 2004; Dubois et al. 2015). Though each rare disease may impact only a small number of patients, collectively they affect over 30M people in the United States. Over half of identified rare diseases affect children and most are considered severe, yet 90% have no therapies available (NORD; NIH.gov). Therefore, substantial unmet medical need remains and addressing these needs should produce societal benefit.

To encourage product development in markets with insufficient profit incentives, governments can introduce a variety of innovation policies and/or offer public sector funding (Bloom, Van Reenen, Williams 2019; Azoulay, Zivin, Li, Sampat 2017). In the context of rare disease drug development, both approaches have been implemented and are considered relatively successful. For example, the Orphan Drug Act of 1983 provides developers with tax credits for R&D costs and extended regulatory exclusivity periods for new products to help firms mitigate financial risks, and the act has been linked to sustained new clinical trial activity and new drug candidate programs in rare disease since its passage (Yin 2008; Gamba, Magazzini, Pertile 2021).[1] Additionally, funding programs have been launched by the National Institutes of Health (NIH) and the U.S. Food and

1 The Orphan Drug Act provides firms with a tax credit for 25% of R&D expenses and two additional years of monopoly-like marketing exclusivity rights if the drug is intended for a disease with fewer than 200,000 U.S. patients. Previously, the tax credit was 50% but was reduced to 25% under the Tax Cuts and Jobs Act of 2017.

Drug Administration (FDA), such as the Rare Diseases Clinical Research Network and Orphan Products Grant Program, and several studies have linked public funding to increases in private sector drug development (Azoulay et al., 2017; Fleming, Greene, Li, Marx, Yao 2019; Cockburn and Henderson 1998). Accordingly, over the last few decades there has been a substantial rise in the number of new private sector products approved for rare diseases (International Rare Disease Research Consortium; FDA.gov).

However, despite increasing interest in rare disease drug development, both innovation incentives and public funding have proven to be only partial solutions to the small market innovation problem as thousands of rare conditions remain unaddressed. Traditional incentives are most effective at inducing innovation for diseases at the margin, such as the conditions with market sizes at the threshold of rare disease qualification where firms stand to reap the greatest financial benefits and the conditions with more advanced scientific understanding where researchers are most likely to secure competitive funding through the NIH's investigator-initiated, peer-reviewed allocation process (Yin 2008; Sampat 2011; Gamba et al. 2021).

Further complicating the expected challenges with small market innovation are the rising costs and complexity of rare disease drug development brought on by the current genomics revolution and advent of precision medicine (Sun, Zheng, Simeonov 2017). In recent years, researchers have discovered hundreds of new rare diseases and identified many of their disease-causing genes (International Rare Disease Research Consortium). Though these explicit advances in scientific understanding should, in theory, render diseases more therapeutically addressable and lower barriers to entry for private sector drug developers, the precision medicine approaches that are most promising in rare disease also require firms to invest in supplemental technology, such as companion diagnostics and genetic screeners, to ensure new products can be appropriately tested in clinical trials

and deployed in the clinical care setting.[2] These extra technology endeavors can add both cost and risk to the existing hurdles that firms face when deciding whether to pursue small market drug development.

Amid ongoing challenges in inducing innovation for rare diseases through traditional government-sponsored incentives, a new type of entity has emerged: the research-focused rare disease foundation (RDF). These foundations are typically formed by highly motivated patients and/or their families after they become frustrated by the lack of available information and the slow pace of research activity within their diagnosed condition. In response, patients and/or their families establish highly focused nonprofit entities with a singular goal of accelerating therapeutic R&D in one disease. Within the literature, the study of this unique type of nonprofit organization and its potential impact on private sector innovation is nascent and limited to a few qualitative case studies. While highly informative, these existing cases offer glimpses into the success of the same few foundations and focal rare diseases (e.g., Cystic Fibrosis, Multiple Myeloma) and are limited in ability to explain the role of research-focused RDFs in inducing private-sector innovation at scale. To my knowledge, no published work has attempted to understand the collective impact of the strategy adopted by these unique nonprofit entities in rare disease.

In this paper, I ask: ***what role do patient-led, research-focused rare disease foundations play in novel therapeutic drug development?*** I answer this research question through a multi-pronged approach that includes: (1) development of a conceptual framework to describe how the organizational strategy employed by RDFs may incentivize firm innovation, (2) construction of a novel case study that illustrates the impact of an RDF on therapeutic development in the associated disease, (3) assembly of a new dataset used to identify RDFs and characterize their research

[2] For example, genetic screening is often necessary to recruit clinical trial participants, trial designs may need to be more complex in order to study the drug in various disease subtypes, and regulatory agencies could require firms to develop companion diagnostics to accompany use of the product in the clinical care setting.

activities, and (4) empirical estimations of the extent to which RDF involvement in the rare disease drug development ecosystem is related to measures of new product development activity.

I define research-focused rare disease foundations (RDFs) as nonprofit 501(c)(3) entities focused on a single disease that operate under a primary mission of finding a curative treatment. Though founded and led by patients and/or their families, these nonprofits are distinct from traditional patient advocacy organizations in their emphasis on research objectives rather than patient support, education and lobbying for public funds. While many RDFs fund traditional research grants, several also take an active role in therapeutic R&D by engaging in complex and sophisticated endeavors not typical for philanthropies. For example, there are more than 50 RDFs in the U.S. that have sponsored development of critical research infrastructure specific to their rare disease, such as biobanks with tissue samples, mouse models, and biomarkers[3]. Nearly 70 of the 149 diseases that I have identified as having operational RDFs have also created extensive clinical trial networks that are equipped to study the disease, executed their own natural history studies, and/or recruited leading scientists to form disease-specific consortia. Most interestingly, at least 40 RDFs have bridged the traditional nonprofit and for profit sector divide by directly engaging with biopharmaceutical partners to collaborate in the clinical stages of product development, lending their resources, disease expertise, and extensive connections to the broader research and patient community.

Conceptually, I argue that the emergence of an active RDF within a rare disease is suggestive of the fact that traditional innovation incentives and public sector funding are, alone, not enough to induce innovation in all rare diseases where demand exists. This is supported by the theory that

[3] As defined in the Nature Portfolio Subjects database, a biomarker is a "biological characteristic that is objectively measured and evaluated as an indicator of normal biological or pathological processes, or a response to a therapeutic intervention". Biomarkers are used in testing of potential drug candidates to define clinical outcome measures and identify patients with specific disease subtypes for trial inclusion.

government alone cannot address all private market failures due to the many heterogenous demands of society and nonprofit intervention often represents an alternative solution (Weisbord 1989). RDFs engage in research within the focal disease to effectively lower the costs of drug development for private sector firms not simply through the provision of additional funding but through systematic de-risking of the steps required to develop a new product. Building on the ideas developed by Feldman and Grady-Reed 2014, among others (Readel 2013; Ramsey et al. 2017; Giusti and Hamermesh 2020; Grady-Reed 2020; Huml et al. 2021), and illustrated through existing success stories of the Cystic Fibrosis Foundation and the Multiple Myeloma Research Foundation, I propose that while funding from RDFs does matter, the strategy these organizations use to deploy their funds is vital in fostering urgent progress toward therapeutic development. First, by creating the research infrastructure in the disease through organization of research priorities, alignment of various actors, generation of data, and creation of critical research tools, many RDFs take on much of the risk associated with early stage development work and limit exposure for firms. Second, once firms decide to enter the disease, explicit collaboration between firms and foundations during clinical development programs offers the potential to speed up average clinical development timelines by providing firms with access to many of these RDF-created resources, which helps firms to avoid common delays that can occur during trial design, site selection, and patient recruitment.

To support this framework, I first combine qualitative and quantitative evidence to develop a novel case study that reinforces the mechanisms RDFs use to encourage drug development efforts. I then use tools from econometrics to test RDF ability to alter the trajectory of drug development in their associated disease. Specifically, I quantify two measures: (1) I begin with a simple exploration of the relationship between RDF spending levels and new clinical trial starts in the disease, which suggests that RDF spending has a statistically significant correlation with new clinical activity. This relationship appears stronger than the relationship between NIH funding and clinical activity. (2)

Then, in the primary empirical analysis, I use a difference in difference framework to estimate the potential effect of RDF organizational strategy on trends in new investment within the disease. This analysis suggests that when the RDF takes an active role in research (via generation of data, creation of research tools, etc.) vs. a passive (grant-funding only) role, the incremental increase in new clinical activity is strongly positive.

Taken together, these contributions conceptualize a role for patient-led, disease-specific nonprofits in addressing a gap in private market innovation that is unable to be fully solved by the public sector. The findings provide clear implications for managers of both research foundations and biopharmaceutical firms. For leaders of rare disease foundations, studies of successful organizations and quantification of their impact on clinical trial activity emphasizes the importance of active involvement in the research ecosystem in achieving their cure-seeking missions. For drug developers, evidence suggests that RDF engagement in research-complementary activities may create a more favorable climate for initiation of rare disease product development.

The reminder of this paper proceeds as follows: in Section 1.2, I establish a clear definition of RDFs, describe how they strategically engage in research, and provide background on rare disease drug development, in Section 1.3, I develop a conceptual framework describing how RDFs adopt a proactive research strategy to effectively lower the costs of drug development for firms and present a novel case study in Spinal Muscular Atrophy, in Section 1.4, I detail the assembly of a novel RDF dataset, in Section 1.5, I discuss the multi-pronged empirical approach for testing the conceptual framework and present and interpret the results, and in Section 1.6, I briefly summarize the paper's implications, limitations and contributions.

1.2 Definitions & Background

1.2.1 Defining the research-focused rare disease foundation

Unlike traditional patient advocacy organizations, research-focused RDFs operate under a primary mission to advance therapeutic development in their focal disease. Identification of a cure is central to the organizational purpose and the majority of its strategic activities foster research activity rather than patient education, outreach, or support. Though research-focused foundations exist across a wide range of conditions with various etiology, severity, and population size, these entities have emerged predominantly within the rare disease ecosystem.[4] In this work, I focus only on foundations operating within rare disease because the incentives for innovation, as well as the economic and managerial implications of rare disease drug development, are often distinct from drug development for more prevalent diseases. Additionally, as noted by Hedge and Sampat (2014), the discreet nature of rare diseases, most of which are genetically linked, allows them to be more easily mapped to measurable variables of innovative activity, such as funding, clinical trials, and therapeutic candidates. Because I create a novel dataset to answer questions about the role of research-focused RDFs within a specific disease, the ability to clearly identify diseases across various data sources is essential for reliable data construction.

Since research-focused RDFs have not been frequently studied in the nonmarket strategy, innovation, or nonprofit literature, I develop a detailed set of inclusion criteria to classify an organization as an RDF. The intent of each criterion is to ensure consistent organizational goals when drawing comparisons across foundations and to allow for measurement in empirical analyses at the disease level. First, the entity must include research and/or therapeutic development within

[4] Though there is no universally agreed upon definition of "rare disease", in the United States rare diseases are conditions that the Food and Drug Administration (FDA) qualifies as "orphan" based on a prevalence threshold of less than 200,000 patients (FDA.gov). The majority (>90%) of rare diseases are thought to be genetically linked (GARD).

their mission statement. Second, the research efforts must be specific to a single rare disease or group of closely related diseases, rather than an umbrella organization focusing across multiple conditions.[5] Third, the entity must be classified as either a private foundation or public charity under the Internal Revenue Service nonprofit tax law, section 501(c)(3) with the most recent Form 990 filing in either 2019 or later (IRS.gov). Fourth, patients and/or their families must have been involved in the initial establishment and ongoing operations of the entity. This last requirement is used to exclude disease foundations formed by academic researchers who are motivated by scientific progress but not necessarily therapeutic development and operate under different timelines than individuals personally affected by the disease. Leveraging this definition, I identify 149 rare diseases with qualifying research-focused RDFs that are operational in the United States. [Appendix A.1 describes the inclusion criteria in more detail and provides examples of organizations that fall within and outside of the definition.]

1.2.2 Patient-Led RDF Establishment

When limited knowledge and research exists within a rare disease, establishment of a research-focused RDF by patients appears to occur in a fairly consistent manner. Interviews with RDF founders coupled with histories of RDF establishment found on RDF websites indicate that the process begins when an individual or their child receives a diagnosis for a rare, poorly understood condition. In an urgent search to identify any clinical research or available treatment options, they become frustrated when no information is available and subsequently recognize an unmet need that they perceive as unaddressed by both the public and private sector. In response, these individuals form a nonprofit foundation with a research oriented mission out of personally-driven urgency to

[5] RDFs can either focus on a single rare disease or a group closely related rare diseases where the underlying science and clinical manifestations are highly consistent and the patient needs are aligned. This requirement allows for more accurate comparison across RDFs by ensuring that RDF missions, activities, and resources are deployed around a singular treatment goal.

drive progress in therapeutic development.[6] Because the incentives for establishment of an RDF are personally-driven (rather than profit-driven) by patients and families directly affected by the disease and emerge from a desire to catalyze seemingly stalled research and development efforts, these entities are no more likely to emerge in diseases with the most promising science, the largest market size, or the highest available funding. For example, in the year prior to RDF establishment, RDFs in my dataset received on average only $3M ($0-45M range) from the NIH and, notably, more than half (58%, n=86) received zero dollars from the NIH, which serves as the largest funder of medical research with an annual budget of around $41.7 billon (NIH.gov).[7] Further, there were on average 57 (0-760 range) scientific articles mentioning the disease published in the year before the RDF was formed, and in 21% of the diseases (n=31) there were zero articles published.[8] As a comparison, multiple sclerosis is also a severe, chronic and progressing condition with a suspected genetic link. The prevalence is around 900,000 patients in the United States or about 4.5 times the rare disease threshold (Wallin et al. 2019). However, multiple sclerosis receives on average, $117M annually from the NIH or 39 times more than the average rare disease and has about 3,000 annual scientific publications or 52 times more.[9] The relative lack of public funding and scientific interest among rare diseases found in my RDF dataset underscores the low research priority in many of the diseases where RDFs subsequently form.

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[6] In cases where the patient family has adequate financial resources, they may establish the RDF as a private foundation, but it is more common for patient families to come together with other highly motivated patients, researchers or clinicians to form the entity together as a public charity. RDFs under both organizational structures interact with the research landscape in a similar manner.

[7] NIH funding within a rare disease was calculated using the online NIH RePorter tool. I searched the disease name (including synonyms) within project abstracts that had secured funding each year.

[8] Scientific publications were calculated by matching each disease name to a Medical Subject Heading (MeSH) term and/or supplementary concept and then performing a search in Pubmed for articles dated the year prior to RDF establishment. Diseases that could not be matched to a MeSH term were excluded. The total number of publications includes any mention of the disease (or synonym) and does not imply that the disease was the topic of the article.

[9] Funding and number of publications reported for multiple sclerosis is the five year annualized average from 2017-2021.

1.2.3 RDF Revenue Sources and Budgets

Most research-focused RDFs are structured as public charities. A review of RDF Form 990 tax filings suggests that public charity RDFs receive the high majority of their funds from direct contributions and gifts (donations). These donations are primarily sourced from patients, their families and members of their communities, and other organizations supporting the RDF mission. Other sources of funds often come from special events, program services, or investment income. Some RDFs also host annual fundraisers, though this strategy is applied less frequently by research-focused RDFs than by the more traditional patient advocacy and support organizations. Very rarely (if ever) do RDFs receive grants from government organizations.

In cases where a patient family has adequate financial resources, they may establish the RDF as a private foundation, which means the organization's funding comes from a single endowment. However, it is more common for patient families to come together with other highly motivated patients, researchers or clinicians to form the entity together. RDFs under both organizational structures interact with the research landscape in a similar manner, though future work could explore whether governance structure may influence RDF effectiveness.

On average, the RDFs included in my dataset spend approximately $4M annually, with a range from $0.4 – 135M and a median spend of $0.5M. A few highly successful RDFs, such as the Cystic Fibrosis Foundation and Multiple Myeloma Research Foundation, have been in operation for several decades and now have substantial resources to spend, which drives up the overall averages. [Note: For data analytic and comparison purposes discussed later in this paper, these RDFs are treated as outliers and not included in the primary empirical analysis.]

1.2.4 Strategic Models of RDF Engagement in Research

To execute on their cure-seeking mission, research-focused RDFs engage in a variety of research-related strategic activities that fall along a "funder – doer continuum" (Giusti and Hamermesh 2020). On the "funder" end, RDFs can adopt a traditional, NIH-style grant funding approach that involves raising money, soliciting project proposals, and distributing funds to the most promising research applications, which are often submitted by university-affiliated researchers. On the "doer" end, RDFs choose to engage more actively in the research ecosystem by proactively identifying gaps in research and barriers to therapeutic development and then providing funding for those specific opportunities or executing them directly through the organization's capabilities. Though historically most patient-led foundations with a research focus have chosen the funder model and operated primarily as grant managers, over the last two decades an increasing number have adopted the more proactive research strategies (Huml et al. 2021; Bakker and La Rosa 2017; Ramsey et al. 2017; deVrueh et al. 2014; Lott 2014; Readel 2013). Notably, since patients establish RDFs in response to a severe lack of scientific and therapeutic progress in the disease, differences in the state of research among diseases where RDFs are formed are minimal and do not appear to be the primary driver of RDF choice in strategy.

The strategic choice to pursue a model closer to the "doer" end of the continuum is fueled by a sense of urgency on behalf of some RDF founders and managers to move away from the typical grant funding success measures, such as number of studies funded and resulting publications, to measures that instead represent tangible advancements toward therapeutic development, such as clinical targets identified and ultimately, percentage of patients with treatment options available.[10]

[10] RDF measures of success are available on foundation websites and in annual reports. More specific measures were also confirmed during informal interviews conducted for this research. For example, leadership from the Castleman Disease Collaboration Network indicated they measure success of the foundation's work based on the percentage of diagnosed patients that have a treatment option available.

More specifically, the majority of RDFs that choose to actively engage in the research ecosystem are still providing funding (often through grants) for early-stage scientific projects, however, the manner in which they deploy the funding and measure its effectiveness differs from passive RDFs that adopt more typical, NIH-style grant funding. For example, instead of putting out a broad call for project proposals in the disease area and selecting the most promising submission to fund, actively engaged RDFs might first identify a specific need in the disease that will move progress toward therapeutic development, such as the identification of a new biomarker or need to collect patient samples to build a research biobank, and then seek opportunities to fund scientists willing to work on that particular initiative. While this approach may seem more obviously aligned with RDF cure-seeking missions, not all RDFs choose this strategy because it requires substantially more time, effort, and industry-specific expertise on behalf of the RDF leadership than execution of the more typical, passive grant funding model that has been deployed widely by nonprofits across industries.

Much of the limited literature describing the role of RDFs in therapeutic development has focused on the clear success of the Cystic Fibrosis Foundation (CFF) and the Multiple Myeloma Research Foundation (MMRF) in steering research activity that led to the approval of several disease modifying therapies within each condition. Both nonprofits anchored their strategy on funding initiatives that linked various stakeholders from academia, biopharma, government and patient communities together under common goals and timelines for therapeutic development (Ramsey et al. 2017). To incentivize participation from industry firms, the CFF adopted a "venture philanthropy model", which differs from nonprofit grant funding in that it involves active project management that is more typical of traditional venture capital arrangements (CFF.org, Feldman and Graddy-Reed 2014; deVrueh 2014; Readel 2013).[11] Rather than invest directly into individual firms, the MMRF

[11] Full descriptions of the venture philanthropy model can be found in Scarlata and Alemany (2010) and Scarlata, Walske, and Zacharakis (2017).

initially focused on generation of robust data and research tools that a variety of firms could leverage in the development of therapeutic candidates, such as a cross-institutional research consortium, a tissue bank to generate genome sequencing data that could be used in target identification, and a clinical trial network to study the disease (Giusti and Hamermesh 2020; Ramsey et al. 2017). Both the MMRF and the CFF are frequently cited as significant actors in the development of the highly efficacious treatments now available within the focal disease, including by the FDA (FDA.gov). Though the execution may have differed slightly, the organizational strategy guiding both entities to achieve cure-seeking missions through proactive engagement within the research and development ecosystems was highly consistent.

1.2.5 Quantification of RDF Research-Complementary Strategic Activities

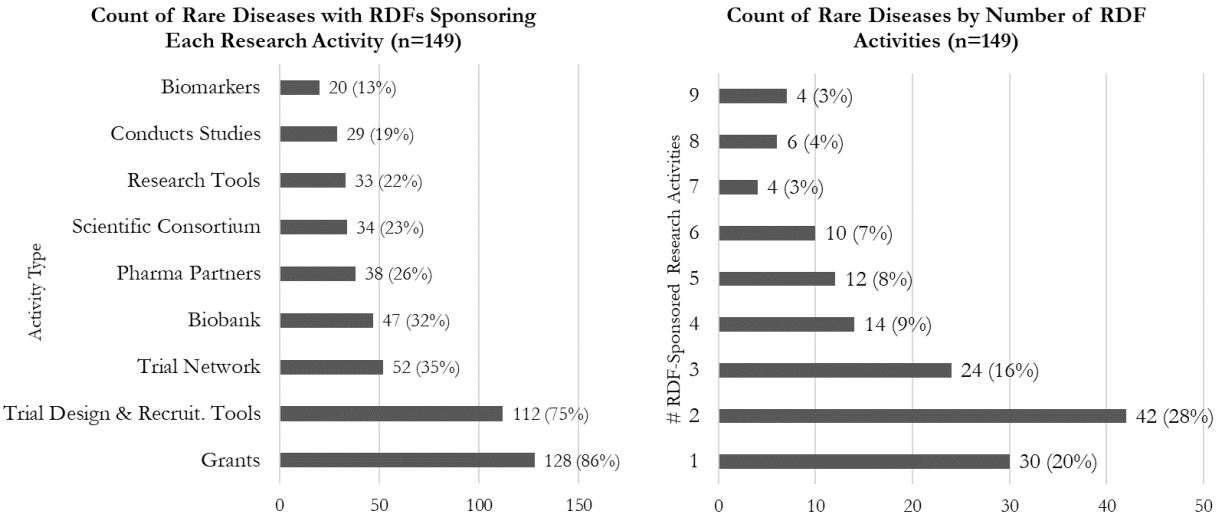
Though perhaps best illustrated by the successes of the CFF and MMRF, many other RDFs are executing complex and sophisticated research activities not typically undertaken by nonprofits. Within my dataset of 149 rare diseases with research-focused RDFs, a majority are funding grants (86%) and creating trial design and recruitment tools, such as patient registries (75%). However, a nontrivial number have also created clinical trial networks (35%), built biobanks for tissue sample collection (32%), partnered explicitly with pharmaceutical firms (26%), created research tools like disease models[12] (22%) and established scientific consortiums (23%). Though less frequent, it is also not uncommon for RDFs to conduct their own studies to understand the natural history and progression of disease (19%) or start biomarker development programs (13%).[13] Additionally, RDFs choosing to engage in research activities beyond grant funding do not appear to specialize in one

[12] Per Nature Portfolio Subjects database, disease models are defined as "animals or cells displaying all or some of the pathological processes that are observed in the actual human or animal disease".

[13] I collected data on specific activities conducted at the organizational level through a systematic manual review of foundation websites, press releases, and periodic community newsletters. Robust organizational information is available from public sources due to the nonprofit status of RDFs.

particular activity but rather execute broadly across as many engagements as resources and time allow. For example, 52% appear to pursue three or more of the activities mentioned above.

Figure 1.1 Count of RDF Research-Complementary Activities



Notes: 1. Grant funding is not counted as one of the eight research-complementary activities because this practice is typical of traditional nonprofits. 2. Creation of trial design and recruitment tools includes patient registries.
Source: Author's dataset.

1.2.6 Rare Disease Drug Development Considerations

The for profit sector is critical in the development and commercialization of therapeutic products (Chakravarthy et al. 2016). However, due to the high costs, substantial risks and lengthy timelines associated with drug development, biopharmaceutical firms must carefully weigh tradeoffs when determining whether to invest in a disease (Lakdawalla 2018; Scott-Morton and Kyle 2011). In the simplest terms, the present value of the potential payout must be greater than the present value of expected development costs. The potential payout is a function of the number of patients, price, and expected years of market exclusivity (or remaining years of patent protection) once the product is approved. The costs involve scientific identification of therapeutic candidates, extensive preclinical and clinical testing programs, preparation of regulatory materials, manufacturing and scale up, and ultimately, product commercialization.

The cost benefit analysis that firms consider when making new product investment decisions is particularly challenged for drug development in rare diseases where patient populations are small (fewer than 200,000 in the U.S.), awareness is generally low, and few, if any, of the scientific tools needed for drug discovery are available. Further, the recent onset of precision medicine and the advancement of science to support targeted therapy development has introduced both new opportunities and challenges for drug developers pursuing rare disease indications. Though several government incentives have attempted to encourage private sector innovation in rare diseases, the structure of each incentive encourages firms to engage in diseases closest to the prevalence threshold for rare disease qualification and in diseases with more advanced scientific understanding where peer-reviewed proposals are most likely to receive funding. Unmet need remains as 90% of rare diseases remain without therapeutic options.

1.2.7 Costs & Risks Associated with Drug Development

The average total capitalized cost of bringing a drug to market has been estimated at upwards of $2.6B and a single clinical trial to demonstrate product efficacy can cost more than $346M [$12.2 million-$33.1 IQR] (DiMasi et al. 2016; Moore et al. 2018). These high capital requirements limit the ability for patient-supported research foundations to pursue therapeutic development goals alone and often necessitate involvement from the private sector.

For an industry firm, the investment decision is complicated by the high risk and uncertainty associated with the therapeutic development process. Though firms face many different types of risks in new product development, including nontrivial concerns related to regulatory and commercialization aspects, the primary technical risk is concentrated in the development stage (Heinonen and Sandberg 2008). Development often begins with the need to translate findings from basic science research into potential clinical-stage drug candidates through extensive preclinical

work. This "translational research" is particularly difficult scientifically and an area where both public sector and industry investment have historically been limited.[14] The NIH estimates that up to 90% of early stage (preclinical) research projects will fail before entering clinical testing (NIH.gov; Seyhan 2019). Then, conditional on entry into the first phase of clinical testing, the likelihood of approval for any drug compound is still only 10-12% (Hay et al. 2014; DiMasi et al. 2016). Finally, because the timelines associated with the development stage average 13-14 years, the opportunity for firms to begin recouping investment is years into the future.

1.2.8 Precision Medicine Opportunities & Challenges for Rare Disease

In recent years, progress in genomic sequencing and an increasing focus on precision medicine has created both opportunities and challenges for therapeutic development in rare disease. Following the completion of the Human Genome Project in 2003, advanced DNA-sequencing techniques, known as "next generation sequencing", allowed researchers to identify many of the genes that cause rare conditions (Boycott et al. 2013). Better understanding of the underlying science along with increasing ability to diagnose patients through their genetic makeup rapidly expanded the opportunity for new product creation in many rare diseases.

At the same time, the need to tailor a treatment to a particular patient based on their individual features, an approach called "precision medicine", can add complexity to traditional drug development and influence which diseases firms select for investment (Chandra, Garthwaite, Stern 2018; Stern, Alexander, Chandra 2017).[15] For example, clinical studies for precision medicines may necessitate identification and validation of a new biomarker, which can be thought of as an objective

[14] The gap in resources provided by public and private sectors that occurs during translational research phases has been extensively referred to as the "Valley of Death" in the medical literature, which is indicative of a key failure point for therapeutic advancement in many diseases.

[15] The FDA defines precision medicine as the tailoring of treatment to an individual's genes, environments, and lifestyle.

indicator of biological response to a therapeutic intervention (FDA.gov). Biomarkers can be used to either measure the efficacy of a potential new product, or to select the patients that are most likely to benefit from the treatment (Sun et al. 2017; Strimbu and Tavel 2010). In the latter case, firms often need to create not only the drug candidate, but also a complementary diagnostic device or product that allows for identification of patients with the particular biomarker, which is called a "companion diagnostic". Further, if biomarkers have not already been identified for the disease, firms may have to undertake additional studies that require both time and resources before advancing any new product candidates into clinical trials.

Beyond the additional scientific and executional complexity associated with development of a precision medicine, tailoring a new product to subpopulations of patients with the disease could further exacerbate the small market challenges facing rare disease drug developers. Even in rare diseases caused by a single gene or gene mutation ("monogenic" disease), the disease may manifest in patients through several different mutational forms and a particular therapeutic product many only work in some of those mutations. For example, one of the first precision medicines approved for a rare disease, ivacaftor for Cystic Fibrosis (Kalydeco®, Vertex Pharmaceuticals), was studied initially in patients with a single mutation of the disease-causing CFTR gene, which occurs in only 2,000 of the nearly 30,000 U.S. patients. Though the drug developer was able to subsequently demonstrate the product's efficacy in additional mutations post-approval, the product is still only marketable to a subset of an already small patient pool (Chandra et al. 2018).

1.2.9 Government Innovation Incentives: The Orphan Drug Act

The Orphan Drug Act (ODA) was passed by the United States Congress in 1983 to encourage for-profit innovation in conditions with small populations by offering firms tax credits for their R&D expenditures (initially set at 50%, lowered to 25% in 2017) and 7 years of marketing exclusivity

vs. the conventional 5 years (Scott-Morton, Kyle 2011). The ODA allows firms to apply for "orphan drug designation" during the clinical testing of a new product candidate when the drug is intended to treat a disease affecting fewer than 200,000 patients in the U.S. (FDA.gov).

The FDA's orphan drug designation theoretically increases innovation in diseases affecting fewer than 200,000 patients through two complementary mechanisms. On the supply-side, tax credits for R&D expenditures in general are considered one of the more effective mechanisms to induce innovation by directly lowering development costs (Bloom, Van Reenen, Williams 2019). On the demand-side, two additional years of marketing exclusivity is thought to increase the expected potential revenue by offering firms a longer period of monopoly-like rights where generic competitors cannot enter and the price of the drug can remain high. Coupled together, these two traditional innovation incentives should encourage firms to begin development in diseases that may have otherwise been deemed poor investment tradeoffs.

Empirical evidence does, in fact, suggest that the ODA increased innovative activity in rare disease (Gamba et al. 2021; Lichtenberg, Waldfogel 2009; Yin 2008). Most notably, Yin (2008) measured new clinical trial activity before and after the passage of the ODA for conditions with prevalence levels under the 200,000 threshold compared with those slightly above the threshold (e.g., "uncommon" but not rare enough to qualify for the orphan designation), and found that the ODA led to an estimated 69% increase in new clinical trial starts for rare disease (<200k patients) vs. uncommon disease (200-500k). However, most of this effect was driven by increases in clinical activity for rare diseases with prevalence levels closest to the threshold, in particular those affecting between 100,000-200,000 patients.[16] Yin explains this finding by suggesting that a fixed tax credit

[16] Specifically, Yin 2008 found a more than 200% increase in trial activity over the "uncommon" control diseases, suggesting that the effect of the ODA is greatest for diseases that fall below but *close to* the orphan designation threshold vs. those that are rarer (<100k).

does not change the marginal revenue of a potential product, so even within the 200k patient threshold, more prevalent diseases are likely to represent higher revenue potential for firms.[17]

The resulting implication is that the Orphan Drug Act does not necessarily steer firms to develop in those conditions with the greatest unmet need, but instead incentivizes new product development in diseases closest to the margin. Many of the most severe rare conditions affect far fewer than 200,000 patients and even with increased opportunity brought on by advances in precision medicine, many diseases continue to have limited interest from drug developers (NORD; GARD).

1.2.10 Government Innovation Incentives: Rare Disease Funding Programs

In addition to tax credits and exclusivity extensions, the public sector has also attempted to catalyze rare disease drug development through direct provision of funding. The Office of Orphan Product Development (OOPD) has introduced several programs specifically designed to subsidize development costs for firms and academic researchers, the most notable of which is the Orphan Products Grant Program. These competitive grants provide recipients with funding to support the cost of clinical trials (in total $15.5M is available annually) evaluating rare disease drug candidates, and though no studies have quantified the impact of this program on increasing rare disease innovation, funded grants through have been linked to the approval of at least nine rare disease products during 2007-2011 (Miller et al. 2020). In recent years, the NIH has also increased its funding for rare disease research, allocating $31M in grants in 2019 to projects that address disease causes, progression, and potential therapeutic targets (NIH.gov).

[17] In fact, studies have also found that at least some portion of the innovation increases attributed to the ODA are a result of firms using a practice called "indication-subdividing" or "disease-slicing", which involves choosing to develop products for sub-populations of more common diseases that otherwise would not have met the rare disease threshold to reap the financial benefits of the ODA (Yin 2009; Gibson and von Tigerstrom 2015).

Though availability of funding in general may increase interest in certain rare diseases, the competitive grant solicitation process used by public sector funding programs incentivizes innovation primarily for a subset of rare diseases where a baseline of scientific progress already exists. Investigator-initiated project proposals allow researchers to select the disease of focus, and since the grant awarding process is peer-reviewed and competitive in nature, projects that represent the best science are most likely to be funded (Sampat 2012). Further, public funding is a limited resource that must be prioritized across many diseases. Unlike the NIH, RDFs have committed all of their resources to a single disease, a factor that makes it easier to fund high risk projects that may be less likely to receive traditional funding (Cholangiocarcinoma.org; Michaeljfox.org).

1.3 Conceptual Framework & Case Study

Though government intervention has historically been the solution to private market failures, such as the small market innovation challenge in rare disease, other institutional forms can also successfully intervene when the demands of society are heterogeneous (Weisbord 1989). Given the thousands of unique rare diseases that affect the population, government incentives alone are unlikely to ever encourage product development in all conditions where patient demand exists (Graddy-Reed 2020; Weisbord 1997). Under this theory, the emergence of a nonprofit entity, like the research-focused RDF, suggests that the existing government innovation incentives are only partial solutions to the dearth of product development in rare diseases. As previously described, RDFs form in response to an absence of scientific progress and research productivity and are fueled by patient urgency to identify treatment options, which suggests at least some level of unmet consumer demand. In addition, though the advent of precision medicine may have expanded the opportunity for rare disease drug development, it has also increased complexity in product development execution.

If research-focused RDFs emerge in response to limited private sector innovation and incomplete government incentives for rare disease drug development, how do these entities intervene to shift market dynamics? The framework that I propose suggests that research-focused RDFs help alleviate some of the risk associated with rare disease drug development for firms by organizing the research community and directly undertaking many of the research activities that are critical foundational aspects of the drug development process. By building the research infrastructure, RDFs are effectively *lowering the cost of drug development for firms* to incentivize new product development in the disease.

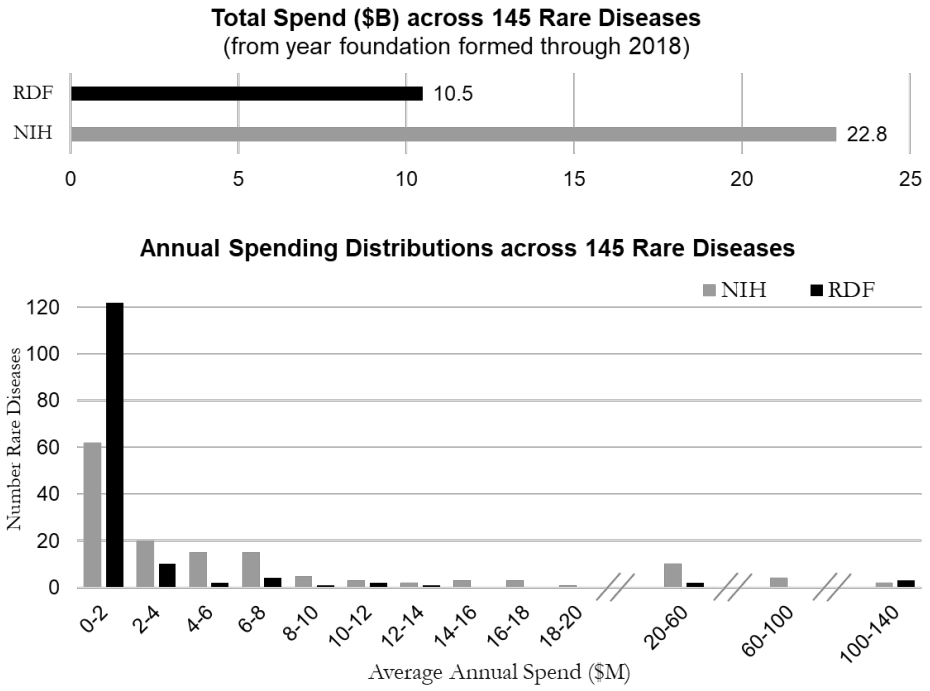
1.3.1 Role of RDFs in Lowering Cost of Development

Patient-led, research-focused RDFs emerge with missions to incentivize therapeutic development in a focal disease that otherwise may not be attractive investments for firms. Unlike government incentives, RDFs shift market dynamics not simply through the provision of grant funding or financial incentives but also through execution of strategic activities that establish a clear development pathway for therapeutic candidates within the disease and attempt to mitigate much of the development risk for firms, which occurs in the translational research and clinical development phases. Alleviation of the many key risks associated with rare disease drug development effectively lowers the cost of drug development.

Recent R&D financing literature suggests that research-focused medical nonprofits are an increasingly critical funder of drug development with growing financial contributions to both academic and industry partners (Grady-Reed 2020; Lanahan et al. 2016; Feldman and Grady-Reed 2014). Though in more prevalent diseases the funding capacity of a patient-led philanthropy often precludes its ability to serve as a substitute for larger funders of research, such as the NIH, RDFs with a singularly focused mission can become the leading funder for the condition (Grady-Reed

2020). For example, in my dataset, research-focused RDFs spent on average 46% of what the NIH spent in the same disease across the same time period, and in 23% of the rare diseases, the RDFs contributed more than the NIH.

Figure 1.2 RDF Spend Compared to NIH Spend by Rare Disease



Source: Author's dataset.

In recent years, drug development firms have become increasingly risk adverse in R&D, and even the availability of substantial funding from an RDF, while helpful, may not be enough to shift investment decisions. Before beginning a research program, firms often want to see evidence of disease understanding, potential therapeutic targets, and a feasible path for patient identification and recruitment during clinical testing. This is particularly important for rare disease where many of the conditions are discreet and genetically linked, potentially limiting the ability for testing of clinical candidates in any supplemental markets. Further, a robust understanding of genetic mutations associated with the condition and identification of biomarkers that can be used to identify the

appropriate patients within whom the therapeutic candidate is most likely to work is critical given the already small patient numbers.

Suppose that by engaging in many of the foundational research activities within the disease and linking together stakeholders across academia, clinical care, industry, and patient communities, RDFs are readying the drug development ecosystem for firms. The resulting implication is that by taking on much of the risk associated with preparing the disease for product development, RDFs limit risk exposure for firms and essentially render investment in the disease more appealing. I hypothesize that this occurs over two stages of the typical drug development cycle:

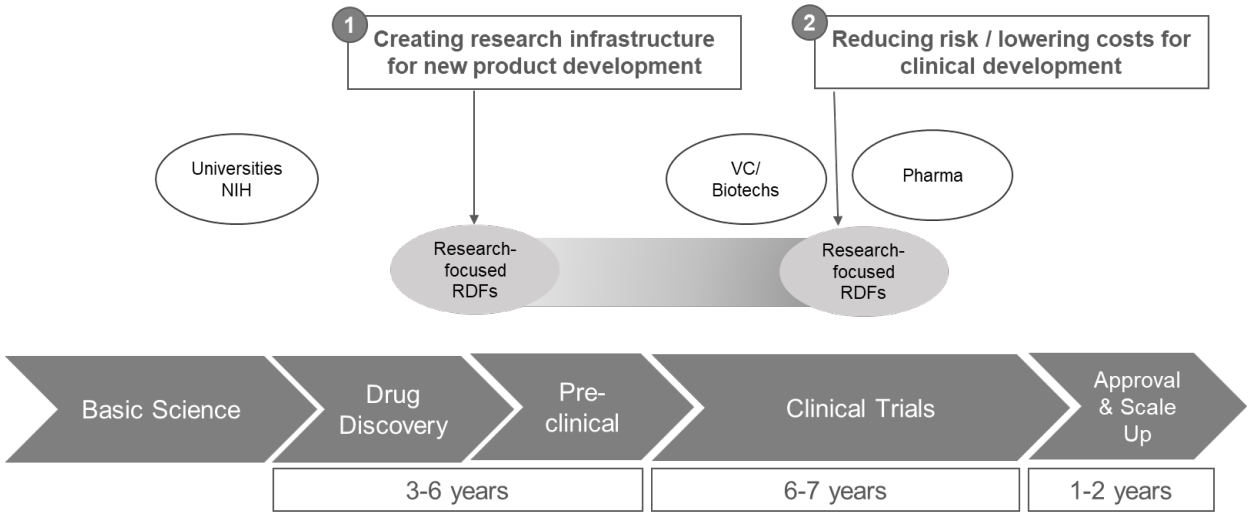
1. The first stage involves RDF-led data generation and research tool development that helps address challenges in bridging the translational gap, which include creation of disease models, scientific consortiums, biobanks, compound screening tools, and execution of natural history studies. The implication is that generation of this critical data and research tools may increase overall investment in the disease because the RDF is lowering the fixed costs associated with drug development for firms (and absorbing some of these costs itself).
2. The second stage involves RDF collaboration with firms during the clinical development phase, which is characterized by usage of these research tools to help firms to avoid common delays. For example, results from natural history studies and biomarker development can be used to design clinical trial endpoints, pre-established clinical trial networks can be used to save time setting up clinical studies, and data-driven patient registries (that include biological data) can be used to speed up recruitment. [Table 1.1 defines these specific research activities in more detail and explains how they influence product development; Figure 1.3 depicts drug development stages where RDFs intervene].

Table 1.1 Explanation of Research Activities Pursued by Research-focused RDFs

Research Activity	Definition / Description	Benefit for Therapeutic Development
1) Formation of scientific research consortiums	Collaboration between cross-institutional researchers and/or research centers that serve as disease experts	• Centralized source of expert advice that can be leveraged across all aspects of development, including trial design and execution
2) Sponsorship of biobanks	Collection of patient biological samples, such as tissue, DNA, or blood, and medical history for research purposes	• Provides researchers with easier access to donated samples used to advance disease understanding • Enables faster study recruitment because patient subtypes can be easily identified
3) Development of scientific research tools, such as disease models and compound screening tools	Animal models with altered genomes to induce human disease state; Biochemical or computational (including AI-driven) screening tools to identify potential drug candidates from a library of compounds	• Necessary for identifying potential therapeutic targets (typically these tools are difficult to access due to intellectual property hurdles) • Used in preclinical testing
4) Identification of disease biomarkers	Objective, measurable indicators of disease presence, severity, or subtype	• Used to define clear, quantifiable clinical endpoints in trials • Used to select patients that are most likely to benefit from the drug (for trial recruitment)
5) Creation of clinical trial networks / centers of excellence	Group of several research centers with established expertise, resources, and protocols for studying a particular disease	• Used to identify clinical trial sites that are experienced and well equipped to study the disease • Enables quicker study implementation
6) Execution of or funding for early stage trials or natural history studies	Collects information about the natural progression of disease in absence of intervention	• Useful in identifying clinical endpoints and patient or observer-reported outcomes • Enables identification of patients subtypes and potential biomarkers based on different disease manifestations that emerge over time • Provides understanding of likely control group outcomes
7) Creation of clinical trial design resources, such as research-driven patient registries and adherence tools	Resources developed with patient input that aid in study design and execution	• More efficient recruitment for trials using existing lists with information on patient subtypes, medical history, and location • Higher retention rates if studies are designed in consideration with patient specific needs
8) Engagement in development partnerships with pharmaceutical firms	Collaborations between firms and foundations through either informal partnerships or venture philanthropy investments	• Offer firms easy access to RDF resources and expertise throughout clinical development • May include provision of substantial capital

Sources: Mayo Clinic Biobank Introduction; Simmons 2008; Sawyer 2005; Strimbu and Tavel 2010; FDA guidance document, "Rare Diseases: Natural History Studies for Drug Development, 2019.

Figure 1.2 Stages of Drug Development Where RDFs Intervene



Source: Author depiction of RDF intervention points along the standard drug development process.

1.3.2 Case Study: The Spinal Muscular Atrophy Foundation

In this section, I illustrate how RDFs can engage in each of these stages through a novel case study of the Spinal Muscular Atrophy Foundation.[18]

Spinal muscular atrophy (SMA) is a devastating genetic rare disease with an estimated incidence of 1 in 6,000-10,000 live births and a life expectancy ranging from 18 months to 20 years depending on the subtype (smafoundation.org). In 1995 researchers identified the disease-causing gene, but despite this critical scientific milestone, the relatively high incidence for a rare disease, and the disease severity, research interest remained low and progress toward therapeutic development appeared nonexistent.

In 2003, parents of a newly diagnosed 1-year old started the Spinal Muscular Atrophy Foundation after experiencing frustration with the lack of information available to help them

[18] Information presented in this case study was collected through in-depth interviews with the foundation founders and managers, extensive review of organization internal documents, and interviews with several of the foundation's external partners. Additional details on the SMA Foundation's formation, strategic business model, and industry collaborations is available as part of the Harvard Business School Case 621-112, "The SMA Foundation: Steering Therapeutic Research and Development in a Rare Disease" (Chandra, Lee-Rey, Marra, 2021).

understand their daughter's rapidly deteriorating condition. Rather than focus on patient support as other nonprofits pursued at the time, the SMA Foundation was established with the explicit mission of enabling cure-seeking research.

The SMA Foundation's operational model involved proactively undertaking activities to render SMA more attractive to developers by reducing the risk associated with drug development. Provision of research funding was a cornerstone of the foundation's strategy but rather than solicit grant proposals, the organization recruited the few scientists working in the disease (and related areas) to join their collaborative scientific advisory board. Together, this board identified the key research priorities within the disease that would directly advance therapeutic development and then the SMA Foundation provided funding to execute against those specific objectives. Many of these projects were focused on generating critical tools needed for therapeutic development, such as mouse models, biomarkers, and disease natural history data. The foundation also established a cross-institutional research hub to conduct and disseminate findings from the work and recruited 18 clinical trial sites to form an SMA trial network that was prepared to study therapeutic candidates within the disease. At the same time, the organization hired individuals with expertise in the biopharmaceutical industry to join its board and leveraged this knowledge to develop a clear business case for investment in drug candidates for SMA. The SMA Foundation founders then pitched the disease to drug developers, offering to collaborate and lend the resources that the organization had created to any interested firms.[19]

In the years following the SMA Foundation's establishment, progress toward a cure accelerated rapidly. For example, from 2003 through 2020, over 165 trials had been started in SMA and over 15

[19] Though collaborations varied by the specific industry partner, typically the SMA Foundation engaged in weekly phone calls with the firms to provide access to research labs and foundation-developed tools, offer advice on trial design related to outcome measures and participant retention, connect firms to experts within the disease and clinical sites, and to help firms prepare for FDA meetings.

firms had initiated development projects. Three highly efficacious therapeutics had been approved by the Food & Drug Administration (FDA) and the SMA Foundation had worked directly with the developers of each product, providing access to their vast resources, expertise, and connections.

Interviews with biopharmaceutical managers who worked directly on the drug programs and in coordination with the SMA Foundation consistently suggested that both initial interest in the disease and ultimate success of the therapeutic development programs were attributable to the Foundation's preparation of the research infrastructure in SMA. Specifically, the ability to leverage the foundation's clinical trial network, natural history data, and access their disease experts helped lower the expected risk for firms deciding whether to invest in SMA.

In an effort to further quantify the potential effect of the SMA Foundation's research activity on therapeutic development activity, I undertake an exercise to compare the flow of new clinical trials in SMA to a set of carefully matched rare diseases with similar characteristics during the same time period. Using the rare disease database, Orphanet, I generate several lists of potential disease matches based on factors that may impact product development incentives, such as prevalence numbers, age of onset, disease severity, whether or not the disease-causing gene has been identified, and the level of scientific understanding.[20] I manually fill in missing or inconsistent data with extensive literature reviews of epidemiological analysis, genetic studies, and clinical reports to narrow down the set of possible matches. I then incorporate historical NIH funding data and historical clinical trial activity. I consider the "historical" time period to be the "pre-period" for analysis purposes and calculate this period from the year that scientists first identified the genetic cause of the disease to the year the foundation was formed as a nonprofit entity pursuing missions related to therapeutic development. This process allows me to identify the six closest disease matches based on

[20] Orphanet is a European database of rare diseases maintained by a consortium of academic researchers but includes U.S. specific prevalence estimates for many rare conditions (orpha.net).

known scientific and publicly available data. Though the diseases may still differ on unobservable measures, the extensive combination of data sources alongside rigorous, time-intensive manual evaluation ensures that the disease matches are as similar as possible on the primary characteristics likely to impact innovative activity prior to establishment of the RDF.

Table 1.2 SMA Case Study – Characteristics of SMA & Matched Control Diseases

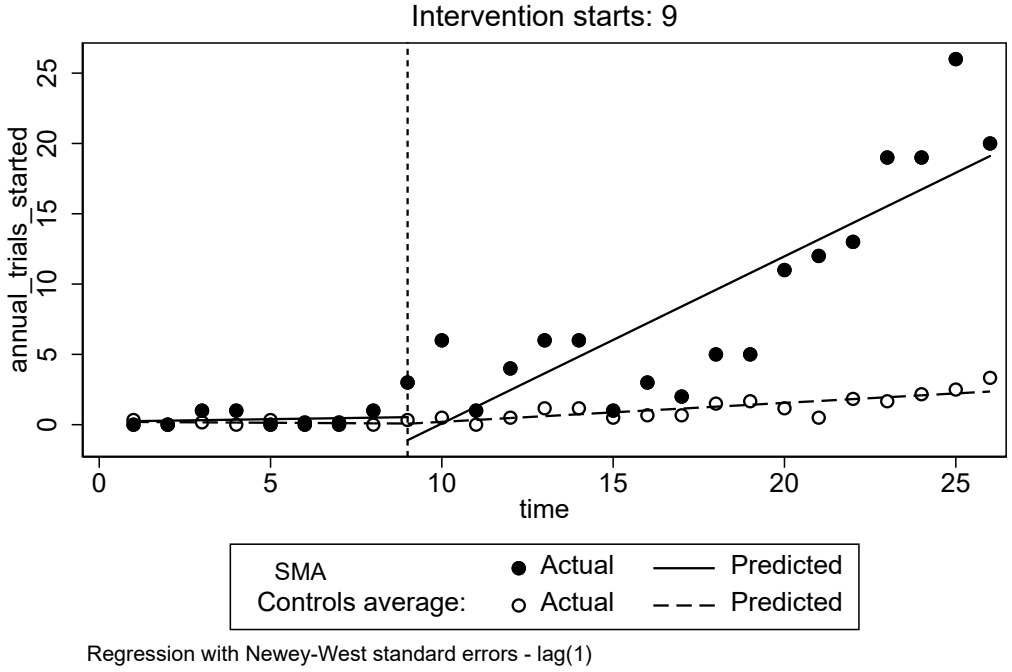
Disease	Est. US Births / Yr	Gene	Age of Onset	Approx. Life Expectancy*	NIH Funding $M, 1995-2002	Trials Started, 1995-2002
Spinal Muscular Atrophy	**340-625**	**SMN**	**Infantile**	**Substantial variation**	**18**	**3**
Marfan Syndrome	585	FBN1	Childhood	30-70 years	13	1
Acyl-CoA dehydrogenase deficiency	585	ACADM	Infantile	Substantial variation	20	0
Galactosemia	200-250	GALT	Infantile	Substantial variation	22	1
Congenital adrenal hyperplasia	250-750	CYP21A2	Infantile	Substantial variation	16	3
Achondroplasia	250	FGFR3	Infantile	50-70 years	25	1
Alport Syndrome	375-750	COL4A	Childhood	40-60 years	24	1

**Approximate life expectancy is affected by a variety of patient-specific factors including disease subtype, severity, age of onset and access to / compliance with treatment. Even when patients survive into adulthood, quality of life is severely impacted due to physical, neurological and psychological impacts of the disease.*

Next, I perform an interrupted time series analysis comparing SMA to the six control diseases and using the year of the SMAF establishment (2003) as the intervention point. Neither the initial mean level difference between SMA and the control diseases nor the difference in the mean baseline slope is statistically significant, which suggests that the control diseases are good comparators for SMA in terms of clinical trial activity (absolute level and trends) in the preintervention period. During the first year of the SMAF's operations, there is no statistically significant treatment effect ($p=0.489$), which is also expected as clinical trial starts resulting from RDF-related activity would not appear immediately. However, over time, there is a statistically significant annual increase in the pre-post trend for trial starts in SMA compared to control diseases ($p<0.01$). Specifically, the treatment group (SMA) increased annual clinical trials started in the postintervention period by 1.19, the control group increased annual trial starts over the same period

by only 0.13, and the difference between them is 1.05 [See Appendix A.2 for details on data collection and regression output].

Figure 1.3 Regression Output – New Clinical Starts in SMA vs. Avg of Controls



The SMA Foundation's role in successfully transforming the research landscape and therapeutic opportunity for patients with the disease provides an example of how RDFs can attract firms to previously unattractive small markets. By organizing the research community and funding development of critical tools to establish the infrastructure for drug development in the disease, the SMA Foundation was able to limit perceived risk exposure for industry drug developers.

1.4 Data

To empirically support the conceptual framework, I create a novel dataset that identifies and describes RDFs and their focal rare diseases. Because there is a lack of collective, organized information documenting research-focused RDFs, the establishment of this data source is a key contribution of my research and will hopefully serve as the basis for many future studies.

1.4.1 RDF Dataset Creation

To identify potential research-focused RDFs, I collated several lists of rare disease patient organizations and performed text based searches of existing databases[21]. This process resulted in the identification of nearly 900 unique patient organizations. Each organization's website was manually reviewed to identify those foundations that focused on a single rare disease (or small group of closely related rare diseases) and explicitly have a research-oriented, cure-seeking mission: this resulted in the retention of approximately 300 entities. Next, I used the GuideStar Pro database to confirm U.S. based operational status as of 2019 and appended organizational tax filings from Form 990s for all available years of foundation operations.[22] This yielded 170 RDFs operating across 149 rare diseases. Publicly available sources for each remaining foundation, including websites, press releases, and newsletters, were then manually reviewed to identify participation in each of eight predefined research activities. These activities included: 1) formation of scientific research consortiums, 2) sponsorship of biobanks, 3) development of scientific research tools, such as disease and animal models, 4) identification of disease biomarkers, 5) creation of clinical trial networks, 6) execution of or funding for early stage trials or natural history studies, 7) creation of clinical trial design resources, such as research-driven patient registries and adherence tools, and 8) engagement in development partnerships with pharmaceutical firms. Whether the RDF solicits grants through a traditional call for proposals was also recorded. [Refer to Table 1.1 for a full description of these research activities].

[21] The initial set of 900 patient organizations was compiled from publicly available lists sourced from FasterCures TRAIN, NORD Patient Organizations, Patient Activation Network (PAN), Rare Disease Clinical Research Network, Rochester Health National Nonprofit Disease Groups. I also performed text searches of the sponsors and collaborators fields in ClinicalTrials.gov and GuideStar Pro database to identify organizations that had "foundation", "consortium", "research alliance", "research network", etc. in the entity's name.

[22] Foundations that spent less than $50,000 for three or more years in a row were excluded from the database because these entities are exempt from 990 filing according to IRS regulations (IRS.gov). Further, the expected impact of organizations that are only able to contribute small amounts to the disease (e.g. $1000 annually) is minimal.

The dataset also includes details on the rare disease in which the RDF operates. Each RDF was first matched to a rare disease recorded in the National Organization of Rare Disease (NORD) dataset. NORD provides basic disease level information, including prevalence estimates, disease severity, genetic links, and importantly, a list of alternate names that may be used for the condition. All of the NORD-based disease names (primary and alternates) were used to search for clinical trials in Clarivate Analytics Cortellis Competitive Intelligence Database, which compiles clinical trials from public registries. I downloaded all trials registered for each rare disease with an operational RDF and recorded fields relevant for this analysis, such as the trial start date.

Finally, NIH funding levels for projects related to the rare disease were pulled from the NIH's online RePORT tool. Disease names, primary and alternate as specified in NORD, were searched in project abstracts and the total amount for projects funded in each year was recorded. These estimates count a project toward funding totals for every disease cited in the abstract, meaning that when early stage projects focus on more than one rare disease, the grant may be double counted. However, the impact of attributing too much project funding to diseases in this manner is expected to be limited given the discreet nature of most rare diseases, which limits opportunity for scientific overlap in many cases. The final dataset contains robust disease and organizational level data on 149 rare diseases with RDFs currently operating in the United States.

1.4.2 Defining Variables to Measure Innovative Activity

In this research, I consider the role that RDFs play in therapeutic development within the focal disease by examining innovation measures specific to the biopharmaceutical industry, such as clinical trial counts and clinical development timelines. A unique aspect of the biopharmaceutical setting is that therapeutic development progress is marked by clear regulatory milestones, particularly at the

clinical stage, and detailed information is available through a combination of publicly available and propriety sources that can be easily accessed.[23]

Within the innovation literature broadly, the most common metrics for quantifying R&D include counts of patent filings, publications, forward citations or research grant awards. However, these metrics best capture the earliest stages of innovation and do not necessarily reflect new investment decisions. My objective is to understand how research-focused RDFs are steering R&D within the disease to find a cure, and though signs of early stage research interest are an important first step in this process, they are not necessarily indicative of therapeutic development. Further, the objectives of RDFs can be in direct contrast to patenting. When RDFs create research tools specific to the disease, the goal is to make these tools as easily accessible to researchers and drug developers as possible without the need to secure intellectual property rights. In fact, RDFs tend to provide access to their research tools, biobanks, and registry data to their partners free of charge or through open access licenses (Chandra et al. 2021). Therefore, I follow the approach of several recently published studies addressing biopharmaceutical innovation (Yin 2008; Hermosilla 2021; Dranove et al. 2014; Arora et al. 2009) and capture measures that are most reflective of investment in and progress toward therapeutic development: new clinical trial starts and clinical development timelines.[24]

[23] For example, clinical trial sponsors are required to register their studies in the National Library of Medicine's publicly-assessible ClinicalTrials.gov database before regulatory approval or publication in any of the International Committee of Medical Journal Editors' publications. Several paid-access databases also capture and aggregate earlier stage research milestones when disclosed by firms in press releases and/or investor reports, such as Cortellis Competitive Intelligence Database, among others. The FDA also publishes a substantial set of regulatory submission documents on its Drugs@FDA website after a therapeutic candidate is approved.

[24] Most recently, Gamba et al. 2021 measure new product investment by counting the annual number of FDA granted orphan status designations at the disease level. This is appropriate for their study which includes all rare diseases listed in Orphanet but does not work in my analysis because I consider only the subset of rare diseases where a research foundation has been established and the total number of orphan designations is zero for most diseases.

1.5 Empirical Approach & Findings

In one potential experiment, I would (nearly) exactly match rare diseases with research-focused RDFs to comparable rare diseases without research-focused RDFs and observe the effect of RDF establishment on trends in new clinical trial starts. The matching algorithm in this hypothetical analysis would consider a variety of disease-level characteristics, such as incidence, age of onset, severity, state of scientific understanding, and research funding levels. These factors would be important to match on to ensure the control group consists of rare diseases that are otherwise similarly primed for clinical activity to those where RDFs have been established.[25] Though in theory this approach seems feasible, in practice, applying this method at scale proves problematic. Creation of a matched control group at the disease level is challenging because: 1) given the rare nature of orphan conditions, most are understudied, resulting in a high degree of variability in the availability and accuracy of information by disease, 2) the existing datasets that do attempt to aggregate rare disease information categorize and name the diseases in a highly inconsistent manner, limiting the ability to compare diseases across data sources without extensive manual interpretation, and 3) the metrics that have not been systematically quantified, including the level of scientific/genetic understanding within the disease and the availability of research funding across multiple sources, are essential considerations for evaluating the readiness of the each diseases for the commencement of clinical trial activity. [In Appendix A.2, I further expand on these limitations].

Due to limitations in comparing innovative activity across rare diseases with and without RDFs, I instead approach the empirical analysis by assembling a series of separate estimations that when taken together, document the relationship between RDF activities and measures of therapeutic

[25] Extensive preclinical studies are often required before any clinical study activity is undertaken in a disease. The ability to conduct preclinical work in a disease is affected by level of scientific understanding and funding availability. The ability to conduct clinical work is dependent on prior preclinical work and on disease-specific factors such as prevalence, age of onset, and severity.

development progress within the focal disease. First, I describe the relationship between total RDF spending levels and new clinical trial starts within the disease to provide a sense for the scale of influence RDFs may have on clinical activity in comparison to the NIH. Then, in the crux of the analysis, I investigate whether the strategy RDFs use to deploy their resources matters, which involves comparing trends in clinical trials activity for disease where RDFs adopt a passive, grant funding research strategy vs. an active engagement strategy that is characterized by involvement in one of the eight previously described research activities. To accomplish this, I look *within* the set of rare diseases that have research-focused RDFs and use variation in RDF strategy and a difference in differences framework to document whether disease with an active RDF experience a greater boost in clinical trial activity post-RDF establishment compared with diseases with a passive RDF. Lastly, I shift focus away from clinical trial counts to measure clinical development timelines. In a retrospective analysis of recently approved orphan drugs, I use difference in means comparisons to preliminarily assess whether drugs developed under firm-foundation collaborations experienced shorter clinical development timelines compared to those developed by firms alone.

1.5.1 RDF Spending & Clinical Activity

Before turning to the primary empirical analysis, I start with an investigation of the relationship between RDF spending and new clinical trial starts to provide a sense for the scale of influence RDFs may have on innovative activity in the disease. In Table 1.3, I use OLS regression to explore the association between total RDF spending in the years from RDF establishment through 2018 and the total number of new clinical trials starts in the disease over the same period. I also consider NIH spending in the disease. To account for right skew of the variables, all variables are log transformed with a small constant (0.01) added.[26] The results suggest that on average, a 10% increase in total

[26] This analysis was repeated using average annualized spending and clinical trial counts as well as using a Poisson distribution rather than log transformed variables and the coefficients were comparable.

RDF spend is associated with an 8.3% increase in total trials started over the period of RDF operation, controlling for NIH spend in the disease ($p<0.01$). Further, the relationship between RDF spending and clinical trial starts in the disease appears about 5 times stronger than the relationship between NIH spending and clinical trial starts over the same time period. [See Figure 1.4 for graphical representation of the relationship between RDF spend and clinical trial starts in the disease; see Table 1.3 for model output and explanation of the variables]. Though causal conclusions cannot be drawn from these associations, the results are, at minimum, suggestive that RDF funding may play an important role in clinical trial activity.

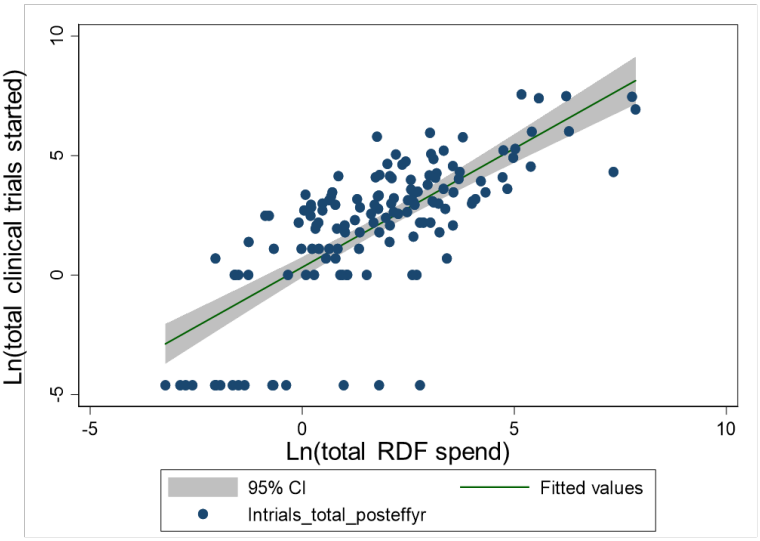
Table 1.3 Relationship Between RDF Spend & Clinical Trial Activity

	Model: (dependent variable is ln of trials starts)		
VARIABLES	(1)	(2)	(3)
Ln total_RDF_spend	0.994**		0.826**
	(0.077)		(0.106)
Ln total_nih_spend		0.546**	0.162*
		(0.061)	(0.071)
Constant	0.330	0.636*	0.199
	(0.215)	(0.254)	(0.220)
Observations	142	142	142
R-squared	0.541	0.365	0.558

Standard errors in parentheses
** p<0.01, * p<0.05, + p<0.1

Notes: 1. Dependent variable is the Ln of total new clinical trial starts in the disease from the year of RDF establishment through 2018. 2. The variable total_RDF_spend is the total RDF spending from the year of establishment through 2018 as reported on Form 990 tax filings. 3. Total_NIH_spend represents the total funding allocated to NIH awarded grants within the rare disease from the year of RDF establishment through 2018.

Figure 1.4 Relationship Between RDF Spend and Clinical Trial Starts in the Focal Rare Disease



Source: Clinicaltrials.gov for clinical trial counts, Guidestar for foundation spending and founding years (form 990s), RePORTER Tool for NIH spending

1.5.2 The Importance of RDF Strategy & New Clinical Trial Starts

Next, I consider whether the organizational strategy adopted by research-focused RDFs may influence new clinical trial starts within the disease. Specifically, I ask whether rare diseases with "active" research RDFs experience a greater increase in clinical trial activity in the years after the RDF is formed compared with rare diseases with a "passive" strategy.

I define "active" research strategy as the pursuit of *1 or more* of the eight innovative research activities noted in Section 1.4.1 and described in Table 1.1. "Passive" strategy is defined as the funding of research grants but no evidence of involvement in any of the eight active research efforts.[27] Notably, "active" strategy *does not* preclude the funding of grants. In fact, the majority of RDFs that fall into the active group also provide grant-like funding for execution of early-stage scientific projects in the disease. The key difference between "active" and "passive" RDFs is that the

[27] In a few cases, an RDF with a passive research strategy may claim to offer a "patient registry". However, many of these registries simply collect patient contact information for informational distribution purposes. To qualify as an "active" research effort, the registry must be data-driven, collecting information about a patient's medical history and diagnosis, and be clearly used to support research related endeavors.

"active" foundations *also* pursue disease-specific research activities aimed directly at the advancement of therapeutic progress. In several cases, active RDFs will use grant funding to steer research efforts toward initiatives that are most critical for therapeutic development by first defining the need (e.g. development of a biomarker, collection of samples for a biobank) and then selecting and funding the scientists willing to execute against these particular objectives.

Since RDFs are established by patients in response to a severe lack of scientific and therapeutic progress in the disease (often a complete absence of such), differences in the state of research within the field do not appear to be the primary driver of RDF strategic choice. Ultimately, the choice to pursue an active vs. passive strategy appears driven by characteristics of individuals founding and leading the RDF. The pursuit of an active strategy requires RDF leaders to invest substantially more time and effort into development of both industry and disease-specific expertise whereas passive strategy is more easily modeled off of typical grant funding structures employed by nonprofits.

1.5.3 Sample Construction

I construct disease-year level panel data from my novel RDF dataset. I include diseases with RDFs established between 1997-2014 to maximize sample size while still allowing for reliable observations of clinical trial starts in a 10 year pre-period and 7-10 year post-period from the year of RDF establishment.[28,29] For comparison purposes, I index the year of RDF establishment to zero. To alleviate concerns that the research infrastructure may be more advanced in some diseases at the time of RDF establishment, I also restrict the sample to diseases with fewer than 20 clinical trials started during the 10 years prior to RDF establishment (an average of <2 trials/year). This filter

[28] 1997 is used as the earliest cutoff date because this is the year the Cystic Fibrosis Foundation launched its Therapeutics Development Program, which is one of the first instances of an RDF pursuing active research strategy. The assumption is that prior to 1997, RDFs pursued research primarily through traditional grant-funding.

[29] In a few cases, RDFs were initially established as patient support groups and later adopted a research-focus. The year of first research activity is recorded as the establishment year. These cases are documented in Appendix A.3.

removes atypical cases where an RDF may have formed later in the cycle of scientific advancement and retains the diseases where there was very limited research progress toward therapeutic development before RDF establishment. As a result, the sample includes diseases where the choice of RDF strategy would have had an opportunity to shape the trajectory of clinical activity. Specifically, the sample includes 1,486 disease-year observations across 66 rare diseases, 28 of which have RDFs that adopted a passive research strategy and 38 an active research strategy.[30]

1.5.4 Data Description

Table 1.4 summarizes characteristics of sample diseases that fall within the active and passive RDF strategy groups. Though the sample includes RDFs formed between 1997-2014, on average RDFs in each group were established within the same two year period (2007-2008). The overall level of new clinical trial activity is, on average, between 2 and 4 trial starts over the entire 10 years before RDF establishment, which falls well below the 2 trials per year inclusion criteria in both groups and suggests that clinical activity was overall very limited before RDF operations began. Further, the number of clinical trials started in the disease that involved an industry firm was, on average, between 1 and 2 over the course of the 10 year pre-period, suggesting that firms did not have existing, active development programs in the rare disease included in the sample prior to RDF establishment.[31] In terms of financial resources, there are small average differences in initial RDF funds (measured as annualized organizational spending over the first 5 years) and in the amount of annual NIH spending in the disease prior to the RDF establishment.[32] Regression estimations

[30] Determination of "active" vs. "passive" research strategy is drawn from my RDF dataset.

[31] Firm involvement is determined from a data field in the Cortellis clinical trial records labeled "Organization Type". Many trials indicate more than one organization type (e.g. "Academic / Company"), and I consider a trial to have firm involvement if a company is listed in any role, such as the lead sponsor or collaborator.

[32] RDF initial spending is collected from annual Form 990 tax filings retrieved from GuidestarPro. NIH spending in the disease is collected from a search for the disease name and its synonyms in the abstracts and titles of funded projects found via the publicly accessible NIH RePORTER tool.

control for these variables in all specifications. Finally, in attempt to approximate the level of scientific awareness for each disease before RDF establishment, I collect data on the number of scientific publications during the five years prior by matching each disease to a Medical Subject Heading (MeSH) term and selecting supplementary concepts when needed to narrow the search. On average, "active" diseases had 19 more publications annually than "passive" diseases prior to RDF establishment, which is small difference given the large range.[33]

Table 1.4 Description of Passive and Active RDF Strategy Groups

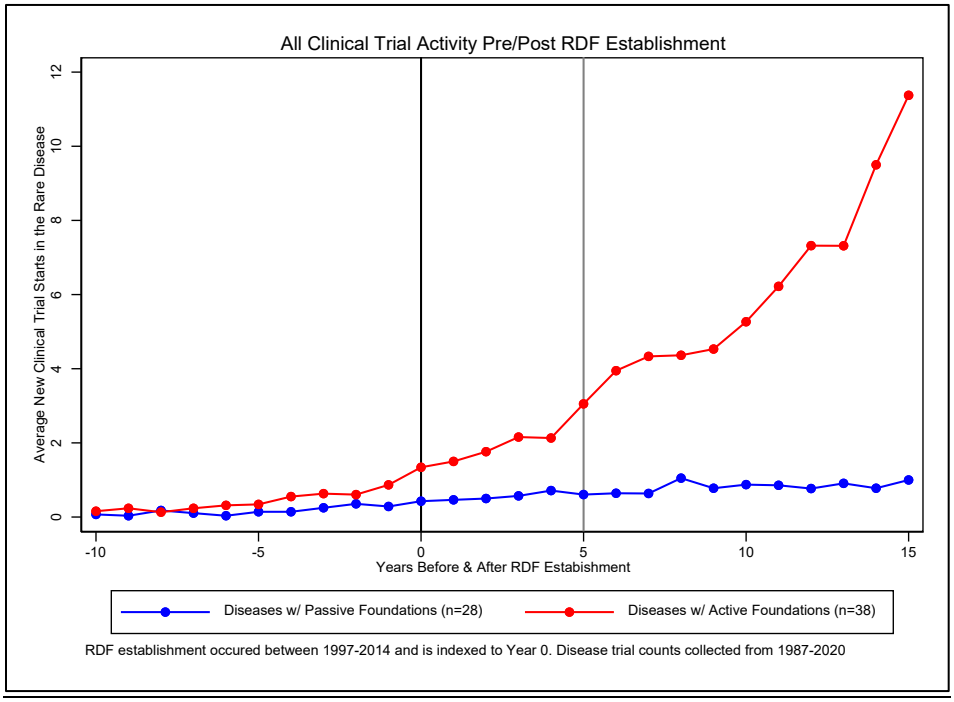
RDF strategy:	PASSIVE	ACTIVE
Number of rare diseases	28	38
Average year RDF established	2008	2007
Initial RDF spend (first 5 year annualized average)	$0.2M [0.0-1.3] range, (0.3) sd	$0.8M [0.0-7.8] range, (1.5) sd
Num of new clinical trial starts before RDF establishment (prior 10 year annualized average)	0.2 trials [0.0-1.0], (0.3)	0.4 trials [0.0-1.7], (0.5)
Num new clinical trial starts before RDF establishment with firm involvement (prior 10 yr annualized avg)	0.1 trials [0.0-0.8], (0.2)	0.2 trials [0-1.4], (0.3)
NIH spend in disease prior to RDF establishment (prior 5 year annualized average)	$1.3M [0.0-15.3], (3.0)	$2.3M [0.0-19.6], (3.9)
Scientific publications prior to RDF establishment (prior 5 year annualized average)	32 articles [0-305], (60)	51 articles [0-302], (59)

Figure 1.5 presents a visual inspection of average trends in new clinical trials starts by RDF strategy group. Panel A considers all clinical trials started in the disease, regardless of the type of sponsor, whereas Panel B considers only those trials that had firm involvement. The graphical views suggest pre-period trends that are consistent and low in magnitude across comparison groups. Differences in average new clinical trial starts between the active and passive diseases do not appear until a few years after RDF establishment and are more pronounced after five years.

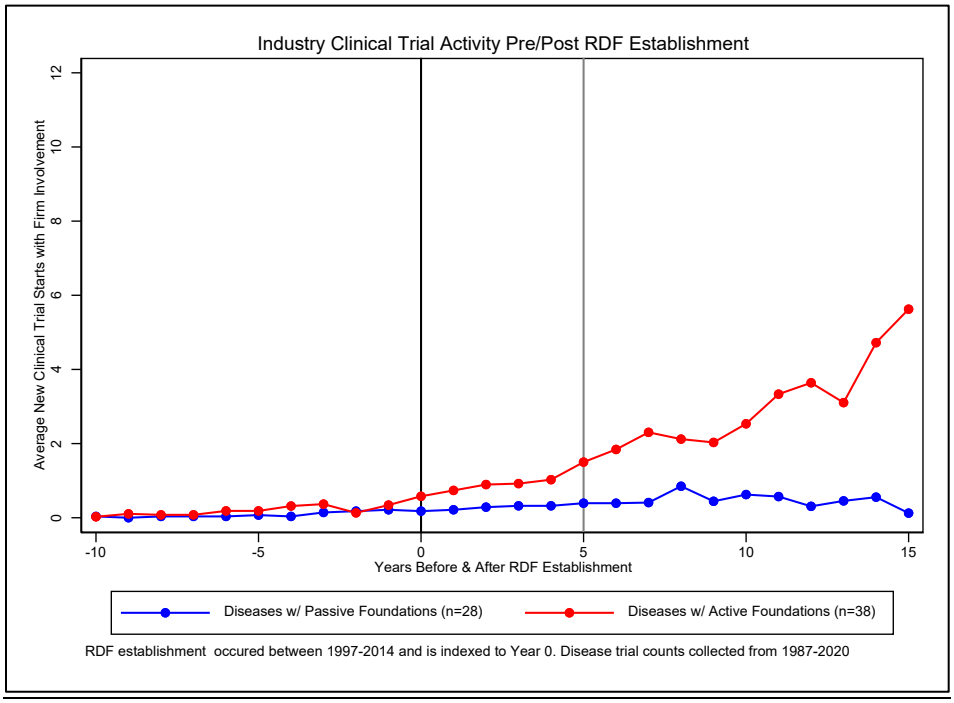
[33] Three diseases could not be matched to any MeSH search term or supplementary concept.

Figure 1.5 New Clinical Trial Starts in Diseases with Active vs. Passive RDFs

Panel A – All New Clinical Starts in the Rare Disease



Panel B –New Clinical Starts with Firm Involvement in the Rare Disease



1.5.5 Empirical Estimations

The empirical analysis uses variation in the type of research strategy executed by RDFs (active vs. passive) to estimate the effect of the strategy on the change in annual number of new clinical trial starts within the rare disease after RDF establishment compared to the period before RDF establishment. Because the dependent variable is right skewed and represents positive count data that includes zeros, I estimate the below Model 1 using Poisson regression with robust standard errors clustered by disease:

$$trialstarts_{it} = \alpha_0 + \beta_1(Active_i) + \beta_2(PostRDF_t) + \beta_3(InitialRDFSpend_i) + \beta_4(PriorNIHSpend_i) + \rho(ActiveXPostRDF)_{it} + \epsilon_{it}$$

where $trialstarts_{it}$ represents the number of new clinical trial starts in disease, *i* and year, *t*, and $Active$ is the indicator for whether the disease has an RDF executing an active research strategy (vs. passive). The $PostRDF$ variable is an indicator for whether the observation year, *t*, occurred before or after the RDF existed and a transition from 0 to 1 represents the establishment of the RDF within the disease. To address selection concerns that RDF choice of organizational strategy may be related to its level of financial resources, I control for initial RDF spending levels in the first five years of operation (using an annualized average). To alleviate concerns that NIH grant funding may be partially driving increases in clinical trial activity, I also control for NIH spending in the disease during the 5 years prior to RDF establishment (also using an annualized average). The coefficient of interest, ρ, is found on the interaction term $ActiveXPostRDF$ and represents the average incremental boost in new clinical trials after RDF establishment for diseases with active RDFs over diseases with passive RDFs. The estimations account for different observation period lengths (between 7-10 years post-RDF establishment). [See Appendix A.3 for descriptions and distributions of all variables used in the empirical specifications].

Though the literature that investigates similar variables at the disease level often controls for disease fixed effects, I find the fixed effects approach to be less appropriate in my scenario and too restrictive in the type of controls that can be included so I include it as a robustness test. For example, because time invariant variables cannot be included, eight diseases are dropped from the Poisson fixed effects model because the dependent variable, new clinical trial starts, remains zero throughout the observation period meaning there were never any trials started for the rare disease. This occurs disproportionally in the passive group (e.g., 7 diseases with passive RDFs are dropped by the model and 1 disease with an active RDF), which is concerning given the already small sample size. Additionally, other disease-specific time invariant controls that are relevant for this scenario, such as the amount of NIH funding the disease received and the number of scientific articles published in the years before RDF establishment, cannot be included in the fixed effects model. Therefore, in the primary specifications presented, I choose to control for the most relevant disease level characteristics and cluster the standard errors at the disease level. As a robustness test, I run Poisson fixed effects models that exclude time invariant controls but include disease fixed effects and find that all coefficients have the same sign and significance. [See Appendix A.3 for fixed effects model output].

Since Figure 1.6 suggests the timing of investment response may be delayed, I explore several additional model specifications in attempt to better understand whether the effect of RDF strategy is observed immediately after RDF establishment or if time is required for the research activities that comprise the strategy to be implemented and to translate into observable changes in clinical trial activity. I follow similar examples in the literature that measure new clinical trial starts and include mutually exclusive indicators for distinct time periods (Yin 2008; Finkelstein 2004). In Model 2, I create a variable indicating whether the observation occurred in the first five years after RDF establishment, $PostRDF_{(years\ 0\text{-}4)}$, and a variable indicating whether the observation occurred five or

more years after RDF establishment, $PostRDF_{(years\ 5\ plus)}$. I interact both variables with *Active* to estimate the incremental effect of the disease having an active (vs. passive) RDF established on the resulting flow of new clinical trials compared to the ten years before RDF establishment. In Model 3, I create a third indicator variable for the five years immediately *prior* to the RDF establishment, $PreRDF_{(years\ -5\ to\ -1)}$, and also interact this variable with *Active* to confirm there were no changes related to eventual RDF strategy in the pre-period. In Model 3, the reference period is the first five years (years -10 to -5) of the pre-period, which occurs between 5 and 10 years before the RDF is established. The equations are below.

Model 2:

$$trialstarts_{it} = \alpha_0 + \beta_1(Active_i) + \beta_2\left(PostRDF_{(Years\ 0-4),t}\right) + \beta_3\left(PostRDF_{(Years\ 5plus),t}\right) + \beta_4(InitialRDFSpend_i) + \beta_5(PriorNIHSpend_i) + \rho_1\left(Active * PostRDF_{(Years\ 0-4)}\right)_{it} + \rho_2\left(Active * PostRDF_{(Years\ 5plus)}\right)_{it} + \epsilon_{it}$$

Model 3:

$$trialstarts_{it} = \alpha_0 + \beta_1(Active_i) + \beta_2\left(PreRDF_{(Years-5\ to\ -1),t}\right) + \beta_3\left(PostRDF_{(Years\ 0-4),t}\right) + \beta_4\left(PostRDF_{(Years\ 5plus),t}\right) + \beta_5(InitialRDFSpend_i) + \beta_6(PriorNIHSpend_i) + \rho_1\left(Active * PreRDF_{(Years-5\ to\ -1)}\right)_{it} + \rho_2\left(Active * PostRDF_{(Years\ 0-4)}\right)_{it} + \rho_3\left(Active * PostRDF_{(Years\ 5plus)}\right)_{it} + \epsilon_{it}$$

where the coefficients of interest are ρ_1, ρ_2 in Model 2 and ρ_1, ρ_2, ρ_3 in Model 3.

Finally, in Model 4, I rerun Model 3 with an additional control approximating the level of scientific awareness of the disease before RDF establishment, which is measured by counting the number of scientific articles in the five years prior. Similar to the controls for initial RDF spend and prior NIH spend, the prior scientific publications variable is reported as a five year annualized average.

1.5.6 Results & Interpretation

Table 1.5 presents the results for Models 1-4. In Model 1, the coefficient on *Active*X*PostRDF* is 0.86, suggesting that RDF establishment led to a 136% increase ($e^{0.857}$-1) in the rate of new clinical trials for diseases with active RDFs beyond that of any increases in the rate of new trials for diseases

with passive RDFs ($p<0.01$).[34] This finding suggests a strong positive relationship between RDF strategy and new clinical trial starts after an RDF is formed when controlling for RDF initial spending and prior NIH spending in the disease. When considering the timing of investment response, the two mutually exclusive post-period interaction terms in Model 2 suggest that any effect of RDF strategy on new clinical trial activity in the disease occurs after the first few years of RDF operation. Specifically, the interaction between $Active$ and $PostRDF_{(Years\ 0-4)}$ is positive but not statistically significant, representing no meaningful difference in the rate of new clinical trials for active vs. passive diseases in the first five years after RDF establishment compared to the years before RDF establishment. However, the interaction between $Active$ and $PostRDF_{(Years\ 5\ plus)}$ is statistically significant ($p<0.01$) and represents a 175% ($e^{1.01}$ -1) increase in the rate of new clinical trial starts for diseases with active RDFs net the increase in rate of trial starts for diseases with passive RDFs. These findings are consistent with the visual divergence between the active and passive groups starting around year 5 that is observed in Figure 1.6.

Model 3, which also includes an indicator for the five years before the RDF establishment, suggests no meaningful difference in the flow of new clinical trials between diseases that were about to (within five years) have an active RDF vs. a passive RDF established. Compared to the 5-10 year period before RDF establishment, the incremental difference in flow of new clinical trials between diseases with active vs. passive RDFs does not appear to materialize until the period five years after RDF establishment.

Finally, in Model 4, which reruns the specification in Model 3 and adds a control for the number of scientific publications prior to RDF establishment, there are no meaningful changes to the magnitude or sign of any of the coefficients.

[34] Since the regressors of interest are binary variables, I discuss the Poisson coefficients in terms of incident rate ratios.

Table 1.5 RDF Strategy & New Clinical Trial Starts, Regression Results

	Model (dependent variable is annual new clinical trial starts)			
Poisson Estimations	(1) Avg Pre-Post Effect	(2) Adding Two Post-Period Estimations	(3) Adding Pre & Post-Period Estimations	(4) Adding Control for Prior Scientific Pubs
Active	0.693+	0.701+	0.693	0.622
	(0.388)	(0.387)	(0.480)	(0.488)
PostRDF	1.394**			
	(0.152)			
$PreRDF_{(years\ -5\ to\ -1)}$			1.012**	1.012**
			(0.343)	(0.343)
$PostRDF_{(years\ 0-4)}$		1.204**	1.833**	1.833**
		(0.171)	(0.296)	(0.296)
$PostRDF_{(years\ 5\ plus)}$		1.508**	2.136**	2.075**
		(0.211)	(0.377)	(0.384)
ActiveXPostRDF	0.857**			
	(0.244)			
$ActiveXPreRDF_{(years\ -5\ to\ -1)}$			0.011	0.036
			(0.430)	(0.431)
$ActiveXPostRDF_{(years\ 0-4)}$		0.269	0.277	0.299
		(0.228)	(0.414)	(0.417)
$ActiveXPostRDF_{(years\ 5\ plus)}$		1.010**	1.019*	1.092*
		(0.289)	(0.488)	(0.492)
InitialRDFSpend	0.054	0.048	0.048	0.036
	(0.050)	(0.050)	(0.050)	(0.052)
PriorNIHSpend	0.074**	0.074**	0.074**	0.049
	(0.015)	(0.016)	(0.016)	(0.031)
PriorPublications				0.002
				(0.003)
Constant	-5.075**	-5.072**	-5.701**	-5.664**
	(0.316)	(0.316)	(0.422)	(0.430)
Number of Diseases	66	66	66	63
Num. with passive RDF	28	28	28	26
Num. with active RDF	38	38	38	37
Observations	1,486	1,486	1,486	1,422

Robust standard errors in parentheses (clustered by disease)

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

From an operational perspective, the lag in observed effect of RDF strategy on new clinical trial activity (Models 2-4) is expected as it can take years for clinical trials to be designed by trial sponsors, approved by Institutional Review Boards, and ultimately implemented at trial sites. Further, many of the strategic activities that characterize the active RDF strategy may also take many years for foundations to implement, such as the creation of a biobank, which involves collection of patient samples, the development of a disease model, which involves scientific experimentation, and the creation of a clinical trial networks and/or scientific consortium, which requires cross-institutional alignment and cooperation.

Notably, this observed lag also provides evidence that active RDFs are not forming only in certain diseases that may be more (or less) ready for clinical trial investment. For example, if the flow of new clinical trial starts began immediately after (or immediately before) RDF establishment, one might speculate that the RDF formed in response to a particular turning point in the scientific progress or resource availability for the disease that rendered it more favorable for clinical investment. The consistent, several year-long lag in investment response, provides evidence to support claims made by RDF founders that they establish these nonprofits out of personal motivation because there is little to no research interest or activity in the disease.[35]

Though the sample size is limited, these estimations suggest that the organizational strategy adopted by RDFs ("active" vs. "passive") does have a strongly positive association with new clinical trial activity in the disease. However, it is difficult to confidently and clearly isolate the effect of the organizational strategy itself because the ability to execute the complex and sophisticated research activities associated with the active strategy may depend on other unobserved factors. Despite this concern, the results of the models presented here are highly suggestive of the fact that organizational

[35] This fact is also supported by the overall low levels of annual scientific articles related to the disease published during the years immediately prior to RDF establishment.

strategy plays an important role in driving new clinical trial activity. RDFs that aim to maximize the use of their available resources should consider pursuing research activities that characterize the active research strategy rather than passive, grant-funding strategy.

1.6 Discussion & Conclusion

New product development decisions in the biopharmaceutical industry require firms to carefully weigh the associated high costs, lengthy timelines and substantial risks against a potential future payout; a tradeoff that can be particularly unattractive in rare disease due to small market sizes and the rapidly changing development landscape brought on by precision medicine. Government initiatives have been somewhat successful in incentivizing innovation in rare disease overall, but the reach of these efforts has been concentrated in diseases where firms and researchers stand to reap the greatest benefit. This is unsurprising because, though we typically conceive of government intervention as the primary means for addressing private market failure, rare diseases represent the many heterogeneous demands of society. More than 7,000 unique rare diseases have been identified; 90% of them remain without treatment options.

In response, a novel nonprofit entity, the patient-led, research-focused rare disease foundation, has formed with an explicit and urgent goal to find a cure for a focal disease. RDFs engage in the research ecosystem in complex ways to effectively lower the cost of drug development by at least partially de-risking the process for firms. First, by establishing the research infrastructure through data generation and tools (e.g., natural history, biomarkers, disease models, clinical site networks) and second, by collaborating with firms in the development process (e.g., connecting firms to the research community, to the trial sites, to the patients).

To support and test this framework, I provide evidence of the relationship between RDF establishment in a disease and new clinical trial starts, which is a critical measure of new investment.

First, I present a novel case study describing how The Spinal Muscular Atrophy Foundation systematically executed these research priorities and collaborated with several biopharmaceutical firms to help bring transformative treatments to market. Then, using newly assembled data, I empirically show that the pursuit an active research strategy is related to increased clinical activity in the disease vs. the pursuit of a passive, grant-funding strategy. These findings suggest that to advance progress toward therapeutic development and attract industry firms to the disease, RDFs should adopt a research strategy characterized by proactive involvement in defining and directing the research priorities within the disease. Further, RDFs should deploy their resources not only to fund investigator-initiated grants but to generate data and create research tools that can be used by industry firms to advance product candidates through the various phases of product development.

This work has several limitations, primarily related to the recentness of the phenomenon and the nascent nature of the related literature. The average year of establishment for the set of currently operating research-focused RDF is 2008, and though RDFs are emerging in new rare diseases every year, it takes several years to observe any effect of their efforts on innovative activity within the disease. Small sample sizes consistently limit the ability to perform more complex empirical analysis as do challenges in identifying appropriate control groups to draw comparisons across rare diseases. The measurement of clinical timelines is retrospective and conditional on successful product approval and not representative of all clinical development projects, the majority of which will fail. However, I attempt to overcome many of these limitations by presenting several pieces of evidence that, though perhaps individually incomplete, collectively describe the relationship between RDF activity and innovation within the focal rare disease. As additional data accumulates with the passage of time and increased operational experience of RDFs, future research can easily build upon many of the preliminary findings presented in this paper.

In conclusion, this research represents the first attempt to study the role of RDFs at scale that focuses beyond their role in financing R&D and instead on the unique organizational strategy they adopt to achieve their cure-seeking missions and shift market dynamics for industry firms. The conceptual framework and supporting findings provide clarity around an emerging phenomenon in the biopharmaceutical industry that has not yet been explored in the innovation literature. It also provides important contributions to nonmarket strategy by conceptualizing a role for patient-led nonprofits in addressing a gap in private market innovation that is unable to be fully solved by the public sector.

For managers responsible for new product development decisions, the investment thesis for rare disease may be changing as an increasing number of research-focused RDFs emerge and begin to generate disease specific data and create research tools that limit much of the early stage risk for firms. Diseases that were previously unattractive opportunities due to small patient populations and limited disease understanding may quickly become interesting to firms as RDFs begin to organize and direct the research community. Further, firms developing products in rare diseases with research active RDFs should be open and inviting of collaboration in order to most easily take advantage of the disease-specific resources RDFs have created.

Chapter 2 Firm-Foundation Collaborations in Clinical Product Development

Abstract

Patient-led, research-focused rare disease foundations (RDFs) undertake strategic activities intended to remove barriers to the development of new therapies for their focal disease. To urgently achieve their cure-seeking missions, RDFs form partnerships with industry firms. Though recent literature has described this new partnership model through case studies, this is the first study to quantify metrics related to these collaborations that are relevant to firms. In this chapter, I use a retrospective cohort design to compare average clinical development durations for approved, novel orphan drugs that were developed via firm-RDF collaboration to similar drugs developed by firms-only. I find that firm-RDF collaboration drugs spent on average 2.6 fewer years in clinical development than firm-only drugs (5.4 vs. 8.0 years, $p<0.01$). Notably, firm-RDF collaboration drugs rarely spent longer than the industry average in clinical development (7.5 years) whereas this was quite common for firm-only drugs. When considering only certain types of orphan drugs, such as those that target monogenic disease or those that qualify for expediated FDA programs, the difference in clinical development durations between the two groups increases in magnitude and remains statistically significant. These results suggest that RDFs may help firms avoid obstacles in clinical trial execution that typically plague rare diseases, such as challenges with patient recruitment, site identification, and endpoint selection. Since the amount of time spent in clinical development is a major driver of overall R&D cost and a critical budgetary metric, biopharmaceutical firms pursuing development of rare disease therapies should proactively seek partnerships with RDFs whenever possible.

2.1 Introduction

Biopharmaceutical firms are increasingly seeking external partnerships to help navigate the challenging scientific and regulatory environment for new therapeutic development (Deloitte 2017). In particular, the rapid growth of public-private partnerships within the pharmaceutical industry has been a frequent topic of discussion in the literature (Yildirim 2016, Roehrich 2014).[36] Though public-private partnerships typically occur between industry firms and either government or academic institutions, a novel type of public-private partnerships has emerged in recent years: collaborations between biopharmaceutical firms and patient-led, research-focused rare disease foundations (RDFs).

Firm-RDF collaborations involve either foundation provision of the early-stage capital needed to conduct proof-of-concept studies and/or firm access to foundation-established resources that can alleviate some of the risk associated with clinical development programs (e.g., patient-registries, clinical trial networks, disease-specific research tools). To date, the limited existing literature surrounding this emerging partnership type has described successful firm-RDF partnerships through detailed case studies (i.e., de Vrueth 2014; Feldman and Graddy-Reed 2014; Readel 2013). However, no known published work has studied firm-RDF collaborations with an aim toward quantifying product development outcomes that are relevant for biopharmaceutical firms developing new drugs, such as clinical development duration.

In this study, I draw on a newly-created dataset with detailed data on over 150 research-focused rare disease foundations (RDFs) to identify and categorize firm-RDF collaborations in clinical development programs for novel (new molecular entity), orphan drugs that have been approved by

[36] The pharmaceutical industry broadly encompasses pharmaceutical and biotechnology firms pursing development of therapeutic products.

the Food and Drug Administration (FDA). I retrospectively analyze whether the orphan drugs that were developed by biopharmaceutical firms in collaboration with an RDF had different clinical development durations compared to similar drugs developed by firms alone (without RDF participation). To identify orphan drugs developed with firm and RDF collaboration, I search for an explicit, publicly-documented link between an RDF's activities and the associated orphan drug's clinical development program and categorize drugs with a confirmed link as "firm-RDF collaboration drugs." Novel orphan drugs indicated for diseases where an RDF does not exist are categorized as "firm-only drugs."

I find a statistically significant difference between the two groups in average development duration, suggesting that drugs developed under firm-RDF collaborations spent on average 2.6 fewer years in development than firm-only developed drugs (5.4 vs. 8.0 years, $p<0.05$). Notably, the distribution of clinical development durations for firm-RDF collaboration drugs is much tighter than that of firm-only drugs and reveals that firm-RDF collaboration drugs rarely spent longer in clinical development than the industry average for orphan drugs (~7.5 years) whereas development durations for firm-only drugs often spanned 12 or more years. In other words, the difference in average development times is driven by the fact that there is no "long tail" of protracted development timelines observed among firm-RDF collaboration products. In a series of additional comparisons, I rerun the calculations including only subsets of the drugs in each group and find that the difference in average development duration between firm-RDF collaboration and firm-only drugs increases when considering only drugs that target monogenic diseases, non-oncology conditions, or ultra-rare diseases. The difference also holds when considering only the orphan drugs that qualified for one or more of the FDA's expediated development pathways.

These results are practically relevant and clearly actionable for biopharmaceutical firms pursing therapeutic development in rare diseases. The statistically significant shorter average development durations coupled with the observation that firm-RDF collaboration drugs rarely spend longer than industry average in development suggests that RDFs may be helping firms avoid delays that commonly occur in clinical trials and lead to multiyear extensions. This hypothesis is supported by the fact that RDFs strategically pursue research-oriented activities explicitly designed to build the infrastructure for efficient clinical development. In fact, many RDFs have a sole mission to generate resources and data that firms can use in the development of novel drugs intended to treat their focal disease. For example, RDFs create data-driven patient registries for use in trial recruitment, form scientific consortiums and research center networks that are already prepared to conduct clinical trials in the disease, and procure natural history data that can be used to inform trial design and select the most appropriate endpoint measures.[37]

The length of time a drug spends in clinical development is a critically important metric for firms because it is a driving factor in overall R&D cost (DiMasi et al. 2016). Current estimates suggest that approximately 85% of clinical studies experience a delay that adds unexpected costs to initial budgets (Avantor Clinical Services). In rare diseases, increased certainty that an investigational drug will not require longer than industry averages for clinical development is likely to be both particularly valuable and particularly salient because small patient populations and limited scientific awareness of the disease renders patient recruitment, study design, and site identification particularly challenging.

While, in theory, firms could undertake research complementary activities aimed at shortening clinical development timelines on their own, RDFs can do so more effectively because of their ability to build strong relationships across the stakeholders that play a critical role in drug

[37] For more detailed explanation of strategic RDF research-activities and engagement within the drug development ecosystem, see conceptual framework discussed in Chapter 1 of this dissertation.

development. First, because RDFs are at the center of the patient community (and led by the patients who are most motivated to participate in research), RDFs can quickly identify and recruit patients to join a research registry and/or donate tissue and DNA samples to a biobank. Additionally, RDFs, as patients themselves, are able to generate excitement and a sense of common purpose around drug development research activities, which in turn may encourage patients to provide details on their disease state that are important for study recruitment but that they might not otherwise be willing to share (e.g. their symptoms, prior treatments, subtype). Second, because RDFs are not concerned with patenting, scientific publications, or revenue generation, they can form working relationships with scientists across sectors - academic, government, and industry. Further, RDFs can foster connections across these various scientific communities, uniting them under the foundation's singular cure-seeking mission. Cross-sector collaborations are essential in setting up clinical trial networks that are equipped to study the rare disease and executing disease-specific studies that generate natural history and biomarker data.

From an economic perspective, RDFs have a singular, cure-seeking mission and so they "profit," or succeed, only when therapies for the focal condition are brought to market. Biopharma firms, on the other hand, are profit-maximizing entities and must allocate resources across diseases to hedge development risk. The acquisition of disease-specific expertise and cultivation of relationships with the patient and scientific communities takes substantial time and resources. While this level of investment may not be economically viable for a biopharmaceutical firm pursuing a single project in the disease, RDFs have multiple opportunities to benefit from the investment – via any current and/or therapeutic development project in the disease.

As a result, partnering with an RDF in the clinical development process can create both time and cost saving opportunities for biopharma firms because RDFs can more effectively execute disease-

specific research activities than firms alone. Therefore, the findings from this analysis suggest managers of biopharmaceutical firms should not only be open to collaboration with RDFs but should proactively seek partnership opportunities with research-oriented RDFs that operate within the targeted disease.

The remainder of this paper proceeds as follows. In Section 2.2, I discuss examples of drugs developed under firm-RDF partnerships from my newly created dataset and elaborate on the relevance of clinical development durations for firms. I describe the methods and data used for this analysis in Section 2.3 and then report the results in Section 2.4. I end with a discussion of the findings and limitations in Section 2.5 and brief conclusion in Section 2.6.

2.2 Background & Relevance

2.2.1 Examples of Recent Firm-RDF Collaborations

Public-private partnerships between biopharmaceutical firms and RDFs can assume varying structures, all of which are formed with the goal of accelerating therapeutic development through collaboration across stakeholders (de Vrueth et. al 2014). The most commonly described partnership model has been termed "venture philanthropy", which is characterized by foundation funding of activities intended to advance cure-seeking missions and ultimately generate returns that can be reinvested toward the organization's activities (Kim and Lo 2019; Feldman and Graddy-Reed 2014; Scarlata and Alemany 2010). Similar to the traditional venture capital model, venture philanthropy within the biopharmaceutical industry often involves direct investment by a disease foundation into an early-stage, pre-revenue firm. This provision of funding provides the foundation with the ability to participate in firm decision-making on product development programs and allows the firm to leverage the RDF's resources that can aid in clinical research, such as a network of scientific experts, established clinical testing sites, and comprehensive patient registries.

Within the pharmaceutical industry, the venture philanthropy model was pioneered by the Cystic Fibrosis Foundation (CFF) in the early 2000's when the foundation invested $150M into Aurora Biosciences (now Vertex Pharmaceuticals) for the development of a novel, disease-modifying therapy (CFF.org, Feldman and Graddy-Reed 2014). The investment occurred at a time when the project was too early-stage and high risk to attract traditional sources of capital and allowed the CFF to work collaboratively with the firm throughout development of the novel therapeutic, Kalydeco®. Since the collaboration was structured like a venture capital deal, the CFF received royalties for sales of the drug once approved, which ultimately generated approximately $3.3B for reinvestment into activities aligned with the CFF's cure-seeking mission (Senior 2015, CFF.org). Following the cystic fibrosis success story, several other disease-specific foundations have also adopted a venture philanthropy model, including CureDuchenne, the Multiple Myeloma Research Foundation's Myeloma Investment Fund, and the EB (Epidermolysis Bullosa) Research Partnership, among others.

RDFs can also enter partnerships with biopharmaceutical firms without engaging in a formal venture philanthropy structure. In some scenarios, the RDF will lead the design and execution of clinical studies and the firm will handle regulatory review and product commercialization. This approach has been successful in ultra-rare diseases where identification of scientific experts and patients eligible for clinical trial participation is particularly difficult for a firm alone to execute. In a recent example, the Progeria Research Foundation, together with Boston Children's Hospital, conducted the majority of the required clinical studies for Zokinvy® (lonafarnib), which in 2018 was the first product approved for Progeria, a disease affecting only 400 children worldwide. The firm with rights to the investigational new drug (IND) license freely provided the drug for early-stage studies. Once proof of concept was established, the Progeria Research Foundation formed a

partnership with Eiger Biopharmaceuticals to fund the pivotal trial. Eiger also led regulatory submission and product commercialization (Eigerbio.com; Progeria Research Foundation).

Finally, firm-RDF partnerships may be structured so that the firm can access the RDF's existing research-oriented resources and leverage the RDF's relationships with other non-industry stakeholders. For example, Blueprint Medicines recently partnered with the Life Raft Group, a patient-led RDF with a mission to identify a cure for gastrointestinal stromal tumors (GIST), during their clinical development of the drug AYVAKIT™ (avapritinib), which was approved in 2020. Blueprint was interested in using the Life Raft Group's existing resources to help with design and execution of the drug's clinical studies, such as the data-driven patient registry and biobank, which the Life Raft Group had built to include over 20 years of patient-reported data on the disease natural history, patient experience, and donated tissue samples (NCI 2020).

2.2.2 Importance of Clinical Development Duration for Firms

The primary measure of interest in this analysis is the length of time a novel, orphan drug spent in clinical development. Since clinical development duration is the driving factor in total cost required to bring a novel drug to market (DiMasi et al. 2016), estimates regarding the expected length and complexity for clinical studies required to obtain FDA approval can impact whether or not a firm pursues development of a drug candidate in a particular indication. In fact, it is not uncommon for firms to terminate drug development programs for strategic business or financial reasons rather than concerns with scientific feasibility (Harrison 2016). [38]

Even with careful planning and calculation of risks, clinical durations often extend beyond initial estimates. Delays in clinical trials are extremely common, affecting an estimated 85% of all clinical

[38] Though the majority of phase 2 and 3 trials fail due to efficacy or safety concerns, ~24% are terminated based on factors within the drug development firm's control, such as operational, commercial or portfolio strategy related concerns (Harrison 2016).

studies (Avantor Clinical Services). The primary reason for delays is related to challenges with patient recruitment and retention. For example, a review of over 400 oncology trials found that nearly 38% failed due to inability to meet enrollment targets (Cheng 2010). Challenges with trial recruitment are even more salient for orphan drug trials because the potential pool of patient participants is extremely limited due to the rare nature of the target disease.[39] In addition to recruitment, several other types of delays are also quite common, including delays related to regulatory requirements, contract and budgetary negotiations, site identification and activation, and general inefficiencies in process and execution (Lai et al. 2021).

In theory, RDFs have the ability to help alleviate many of the challenges with clinical trial design and execution that can lead to unplanned delays. For example, 72% (n=107) of the RDFs identified in my dataset have developed a data-driven patient registry with detailed patient information, such as disease subtype, prior treatments, and demographic data relevant for trial participation (e.g. age, where the patient resides). Additionally, 35% (n=52) of RDFs have established a clinical trial network, which is a group of medical centers and trial investigators that are knowledgeable about the disease and equipped to study it. Other RDF-developed resources, such as biobanks with tissue samples, endpoint data generated from natural history studies, and validated disease models can help firms conduct earlier stage research to inform trial design and selection of outcome measures.

2.3 Methods

In this analysis, I use a retrospective cohort design to compare clinical development durations for novel, orphan drugs developed with firm-RDF collaboration to similar orphan drugs developed by firms only. I also consider factors related to the drug's regulatory status and its targeted disease

[39] Orphan drugs are indicated for rare diseases which are defined as conditions affecting fewer than 200,000 patients in the United States (FDA.gov)

that may impact development durations. The sample includes novel, FDA approved, orphan drugs that are available in the United States.

2.3.1 Orphan Drug Sample Construction

Using FDA documents, I start with the comprehensive set of New Molecular Entities (NMEs) that were approved between 1983-2021 (inclusive) and received orphan designation from the FDA (n=373).[40] NMEs are drugs that contain active moieties that have not been approved by the FDA previously, and orphan designation signifies that the product treats a disease affecting fewer than 200,000 patients in the United States. To keep the sample focused on drug candidates for rare diseases most applicable in the U.S. market, I reviewed the approved indication for each drug and removed drugs with indications intended for developing countries, such as Malaria and Ebola. I also removed diagnostic products and drugs approved for rare complications resulting from a medical procedure, such as transplant rejection, because many development considerations differ for these product types compared to drugs that target chronic, genetic conditions.

2.3.2 Cohort Assignment & Identification of Firm-RDF Collaboration Drugs

I divided the remaining 312 approved orphan drugs into two cohorts based on their rare disease indication. The first cohort includes diseases where an active RDF had been previously identified.[41] Drugs with indications for diseases without an RDF were assigned to the second cohort. Within the first cohort, I then searched across several publicly-available data sources for documentation of explicit RDF involvement in the drug's clinical development process. Specifically, I first reviewed

[40] Orphan designation is a regulatory status established under the Orphan Drug Act that can be granted by the FDA to a therapeutic product that treats a rare disease. Firms can apply for orphan designation while the product is being tested in clinical trials and if the designation is granted, the firm will receive the development incentives provided under the Orphan Drug Act, such as tax credits and extended exclusivity periods upon approval (FDA.gov).

[41] Chapter 1 of this dissertation includes a detailed description of the newly created RDF dataset that identifies all of the patient-led, research-oriented rare disease foundations in the United States that spend at least $50k annually.

each drug's clinical trials that were registered in ClinicalTrials.gov for evidence of RDF involvement as an official collaborator.[42] Then, I searched for biopharmaceutical financing deals (e.g. venture philanthropy investments) involving firms and RDFs within the Cortellis Competitive Intelligence Database.[43] Finally, I performed a comprehensive text search of the firm websites and press releases, foundation websites and newsletters, and FDA statements related to the drug's approval for acknowledgement of a partnership between the firm and the RDF operating in the disease. This process yielded 28 novel orphan drugs approved between 2012 and 2021 (inclusive) that involved confirmed collaboration between the development firm and the RDF. These 28 firm-RDF collaboration drugs were retained in Cohort 1 for data analysis.[44] (See Appendix B.1 for details on all 28 of the orphan drugs developed with RDF collaboration and the specific sources used to verify the collaboration).

During those same years (2012-2021), 95 novel rare disease drugs were approved for conditions that do not have an existing research-focused RDF, and these drugs were classified into Cohort 2. Orphan drugs approved prior to 2012 (n=46) were excluded from the sample because there were no firm-RDF collaborations that resulted in drug approval before this time.[45] In robustness tests, orphan drugs originally assigned to Cohorts 1 and 2 that were excluded from the main analysis because of either an approval date before 2012 or existence of an active RDF in the disease without a publicly disclosed link between the firm and RDF are added back in as subgroups within Cohort 1

[42] ClinicalTrials.gov is a publicly-available database managed by the National Library of Medicine. Trial sponsors are required to register phase 2 and 3 trials for all FDA-regulated therapeutics.

[43] Cortellis is a paid-access database offered by Clarivate Analytics that aggregates biopharmaceutical industry data from a variety of sources.

[44] 32 orphan drugs developed in rare diseases with an active RDF but where no explicit link between the RDF and development firm could be found were dropped from Cohort 1.

[45] Kalydeco® approved in early 2012 was the first example of a firm-RDF developed drug to gain FDA approval.

and 2. These results are reported in Appendix B.2 and do not differ from the findings in the main analysis.

2.3.3 Calculation of Clinical Development Duration

To calculate the length of time each drug assigned to Cohort 1 and Cohort 2 spent in clinical development, I count the total number of days that the drug developer (biopharmaceutical firm) spent conducting clinical testing and preparing regulatory documents. I do not include the time that the FDA required to review the drug application materials. Therefore, clinical development durations reported in this paper represent only the time in which the drug developer was actively testing the drug and preparing for regulatory submission and are not affected by the FDA's standard vs. priority review timelines.[46] The commencement of this period is clearly defined by the filing of an Investigational New Drug Application (IND), which occurs when the developer determines they have collected enough preclinical evidence to begin clinical testing in human trials.[47] The completion is marked by submission of either the New Drug Application (NDA) for small molecule drugs or Biologics License Application (BLA) for biologic products, which includes a robust set of evidence collected from clinical studies that support the drug candidate's case for FDA approval.[48]

All regulatory filing dates were obtained from FDA approval documents uploaded to the Drugs@FDA website. Because the IND dates are not reported consistently in the database, I used a combination of text searching and manual review to parse several of the published FDA documents

[46] Under the PDUFA agreement, the FDA has 10 months to review a new drug application after it is submitted by the developer, unless the drug has been granted priority review which shortens this period to 6 months.

[47] Clinical testing can begin 30 days after the drug developer files an IND with the FDA unless the FDA places the application on clinical hold due to concerns with the preclinical evidence provided.

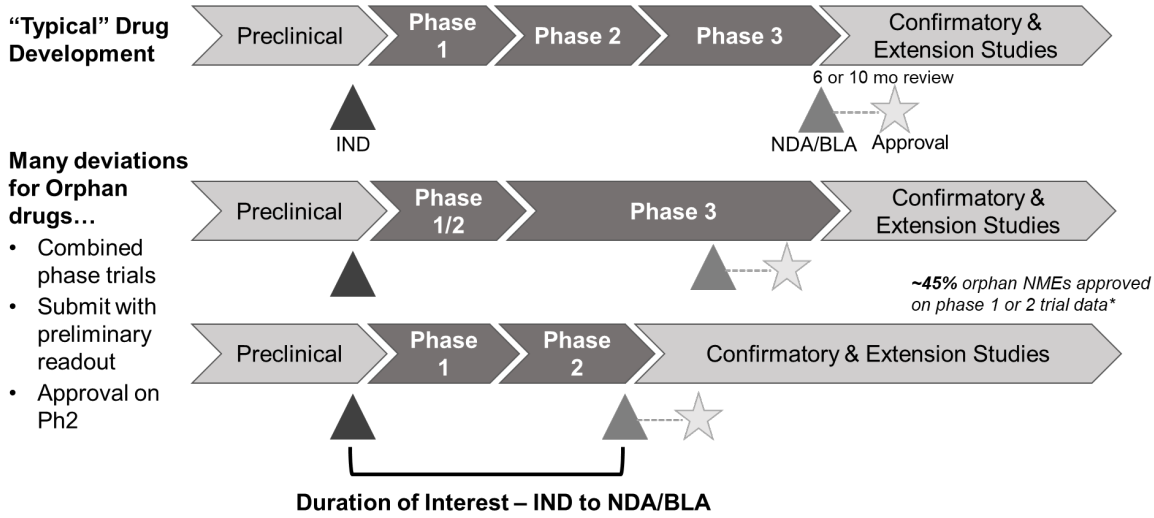
[48] After the drug developer submits an NDA/BLA, the FDA has 10 months to review the application to determine eligibility for approval or request additional information be generated (called the PDUFA date). In cases where the drug has received priority review, the timeframe is shortened to 6 months (FDA.gov).

for each drug.[49] To validate IND dates, I replicated the methodology used by Audibert, et al. (2017) by searching drug names on the Federal Register, which publishes an official determination of the drug's regulatory review timeline whenever the drug developer files for a patent extension.

In the ideal analysis, I would measure not only the overall clinical development duration but also incremental milestones that occur during the clinical development phases, such as the length of individual clinical trial phases, to pinpoint the specific areas where firm-RDF collaborations may be different from established averages. However, orphan drugs rarely follow the standard regulatory pathway (e.g. Phase 1, Phase 2, Phase 3) because of several FDA-sponsored programs that allow for expediated development in diseases where there are few, if any, existing treatment options. For example, approximately 45% of novel orphan drugs were approved using data from either a Phase 1 or Phase 2 trial, which means commencement of a Phase 3 study was not required before submission of the NDA/BLA (IOM Committee on Accelerating Rare Disease Research & Orphan Product Dev). These deviations from the standard drug development regulatory pathway suggest the most appropriate method for comparing clinical development durations across drugs is to use the timeframe from IND filing to NDA/BLA submission. Figure 2.1 depicts the clinical development pathway and some of the common deviations observed in rare disease drug development.

[49] The IND dates were most commonly found in the Summary Review or the Medical Review files but occasionally identified in other correspondence documents. Documents were uploaded by the FDA in PDF form and though most were text searchable, some were scanned copies requiring detailed reading.

Figure 2.1 Clinical Development Pathway and Common Deviations for Orphan Drugs



*Source: IOM Committee on Accelerating Rare Disease Research & Orphan Product Dev. National Academies Press, Washington D.C. 2010.

Since the outcome measure of interest in this analysis is the total time an orphan drug spent in clinical development, I consider only drugs that were successful in achieving FDA approval. As designed, the analysis does not include drugs that failed during development or the likelihood of success of drug approval given firm-RDF collaboration. While likelihood of success is a meaningful measure for both firms and RDFs, limitations in available data and the manner in which firm-RDF collaborations are disclosed prevent inclusion of "failed" drugs. Specifically, it is extremely challenging to verify RDF involvement in early-stage drug development programs because firms generally do not disclose details about a drug's clinical development, including any partnerships with an RDF, until after the drug's approval.[50] Additionally, availability of "start dates" for clinical development (IND filing date) is only made public for drugs after approval, which means this information is not available for drugs that fail to advance in clinical development.

[50] In most documented cases, firms disclose clinical development partnerships with RDFs in press releases announcing a drug's FDA approval or on the firm website describing the approved drug.

2.3.4 Additional Drug-Specific Data Collection

In addition to key regulatory filing dates, information was collected for each orphan drug in Cohort 1 and 2 to inform the analysis, including the drug's qualification for FDA expediated programs and factors related to the rare disease in which the drug is intended to treat.

While the FDA offers a variety of expediated programs for investigational drug candidates, the majority of these programs impact the review and approval timelines, which occur after the drug developer has submitted an NDA/BLA. Therefore, programs that influence only review timelines are not relevant in this analysis because clinical development duration is measured from IND filing to NDA/BLA submission. However, two important exceptions are Accelerated Approval and Breakthrough Therapy Designation (BTD). Accelerated Approval allows drugs that fill an unmet medical need to be approved based on a surrogate endpoint, which the FDA defines as a marker that is thought to predict clinical benefit but is not itself a measure of clinical benefit.[51] In theory, the use of surrogate endpoints can allow developers to more quickly gather the required amount of evidence to submit an NDA/BLA to the FDA, particularly when observation of the clinical benefit may take years. Breakthrough Therapy Designation also has the potential to speed up clinical development timelines by offering developers of drug candidates intended to treat severe disease the opportunity to engage more frequently with the FDA throughout the testing process on issues such as trial design and data collection.[52] Since both the BTD and Accelerated Approval may provide regulatory-sponsored opportunities to speed up clinical development timelines, I collect information about each drug's BTD and Accelerated Approval status from regulatory filing materials.

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[51] The following example of a surrogate endpoint used for accelerated approval is provided by the FDA: "…instead of having to wait to learn if a drug actually extends survival for cancer patients, the FDA may approve a drug based on evidence that the drug shrinks tumors, because tumor shrinkage is considered *reasonably likely to predict* a real clinical benefit." (FDA.gov).

[52] Surrogate endpoints can also be used in trials for Breakthrough Therapy designated drugs if the endpoint if the surrogate endpoint suggests effect on serious symptoms (FDA.gov).

Finally, relevant disease-specific characteristics that may influence clinical development durations, such as prevalence, the genetic nature of the disease, and whether the disease is oncology related were collected for each drug. Though all drugs included in the sample are "rare", the diseases that affect fewer than 1 in 50,000 (equivalent to about 6,500 U.S. patients) can be considered "ultra-rare", a distinction that is important to consider because trial recruitment may be more difficult when so few patients exist (National Institute for Health and Clinical Excellence).[53] Diseases were also classified as monogenic or polygenic depending on the number of disease-causing genes. In theory, monogenic conditions may be at least somewhat easier to target with gene therapy, though this claim has been debated (Gewin 2015). Finally, diseases were classified as oncologic or not since oncology indications have been increasingly studied using novel trial formats (Dhingra 2020). I collect all of this disease-specific information by searching each drug's indicated rare disease in the National Organization of Rare Diseases (NORD) and Orphanet databases.

2.3.5 Method for Comparing Differences in Clinical Development Durations

To compare the average length of time drugs in Cohort 1 and Cohort 2 spent in clinical development, I use a series of two-tailed difference in means tests.[54] I compute the difference for the overall sample and for relevant subsets of each cohort, such as only the monogenic drugs, etc. I also plot the distributions for each cohort to examine differences in trends and identify any outliers or drivers of differences in the averages.

[53] Ultra-rare diseases are defined in Europe as affecting fewer than 1 in 50,000 people.

[54] Comparisons presented use a two-tailed t-test because the sample sizes are small. When rerun using a two-tailed z-test, there is no change to any of the findings.

2.4 Results

2.4.1 Data Description for Cohorts 1 & 2

Table 2.1 describes characteristics of the novel orphan drugs included in Cohorts 1 & 2. Though the sample sizes vary (n=28 for Cohort 1 and n=95 for Cohort 2), the distributions are relatively similar across the key metrics that can influence drug development timelines. The firm-RDF collaboration drugs (Cohort 1) are slightly less likely to be oncology products and target ultra-rare disease, though these differences disappear when considering unique diseases within each cohort rather than unique drugs (see Appendix B.3). Cohort 1 drugs are somewhat more likely to target monogenic disease. The percentage of drugs receiving breakthrough therapy designation and accelerated approval is constant across cohorts. However, a slightly higher percentage of Cohort 1 drugs received at least one of these two regulatory designations (either Breakthrough Therapy *or* Accelerated Approval).

Table 2.1 Cohort 1 and 2 Descriptive Statistics

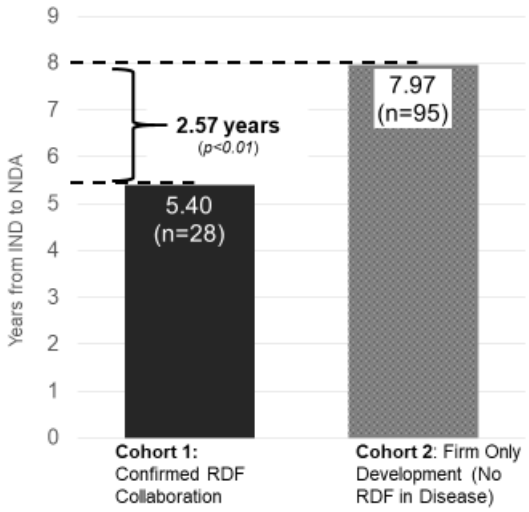
	Cohort 1	**Cohort 2 (Comparison)**
Description	Orphan NMEs developed with confirmed RDF collaboration	Orphan NMEs with no RDF active in the disease
Approval Period	2012-2021	2012-2021
Total NMEs NDA BLA	28 75% (21) 25% (7)	95 72% (68) 28% (27)
Oncology	43% (12)	52% (49)
Genetic Monogenic	100% (28) 46% (13)	97% (92) 21% (20)
Prevalence Ultra-rare* Rare	 18% (5) 82% (23)	 26% (25) 73% (70)
Breakthrough Therapy Des. Accelerated Approval (Either)	46% (13) 36% (10) 75% (21)	46% (44) 38% (36) 59% (56)

*Ultra-rare is defined as fewer than 1 in 50,000 (~6,500 U.S. patients).

2.4.2 Cohort 1 & 2 Difference in Means

Overall, the average length of clinical development as measured from IND filing to NDA/BLA submission is 7.45 years for all orphan drugs in the sample. This is closely aligned with prior published estimates of orphan NME drug development durations, which average 7.5 years (Tufts Center for the Study of Drug Development). The average length of clinical development was 5.4 years for drugs developed with firm-RDF collaboration (Cohort 1) and 8.0 years for drugs developed by firms alone (Cohort 2). This results in a 2.57 year average difference, which is statistically significant using a two-sided difference in means test ($p<0.01$).

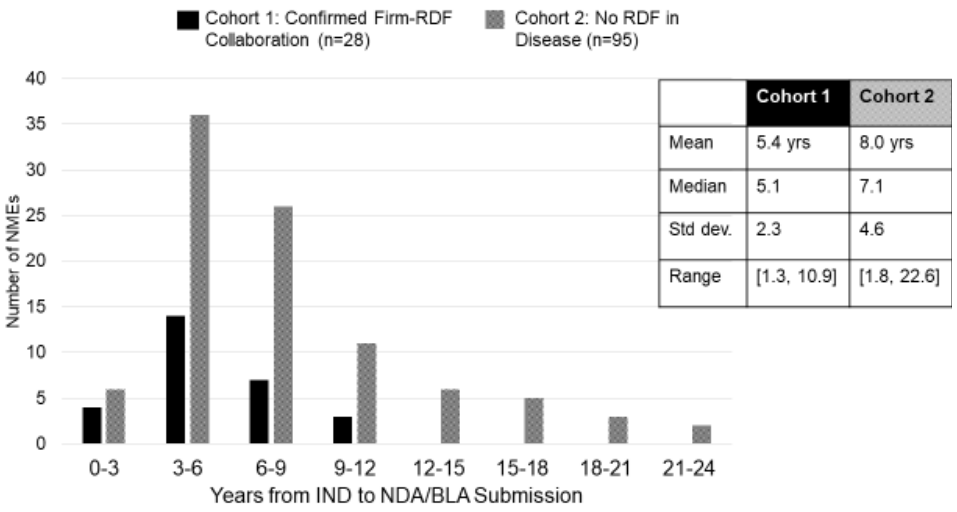
Figure 2.2 Average Clinical Duration Years (IND to NDA/BLA) for Orphan NMEs



Notably, examination of the distributions for clinical development timelines across Cohort 1 and 2 drugs suggest that drugs developed with firm-RDF collaboration are more likely to fall closer to the average expected timeline. In fact, no drugs in Cohort 1 spent longer than 10 years in clinical development. In contrast, the distributional spread for drugs developed by firms alone (Cohort 2) is

much wider and many of these drugs spent much longer than average in development (e.g., between 12-20 years).[55]

Figure 2.3 Clinical Development Duration Distributions for Orphan NMEs

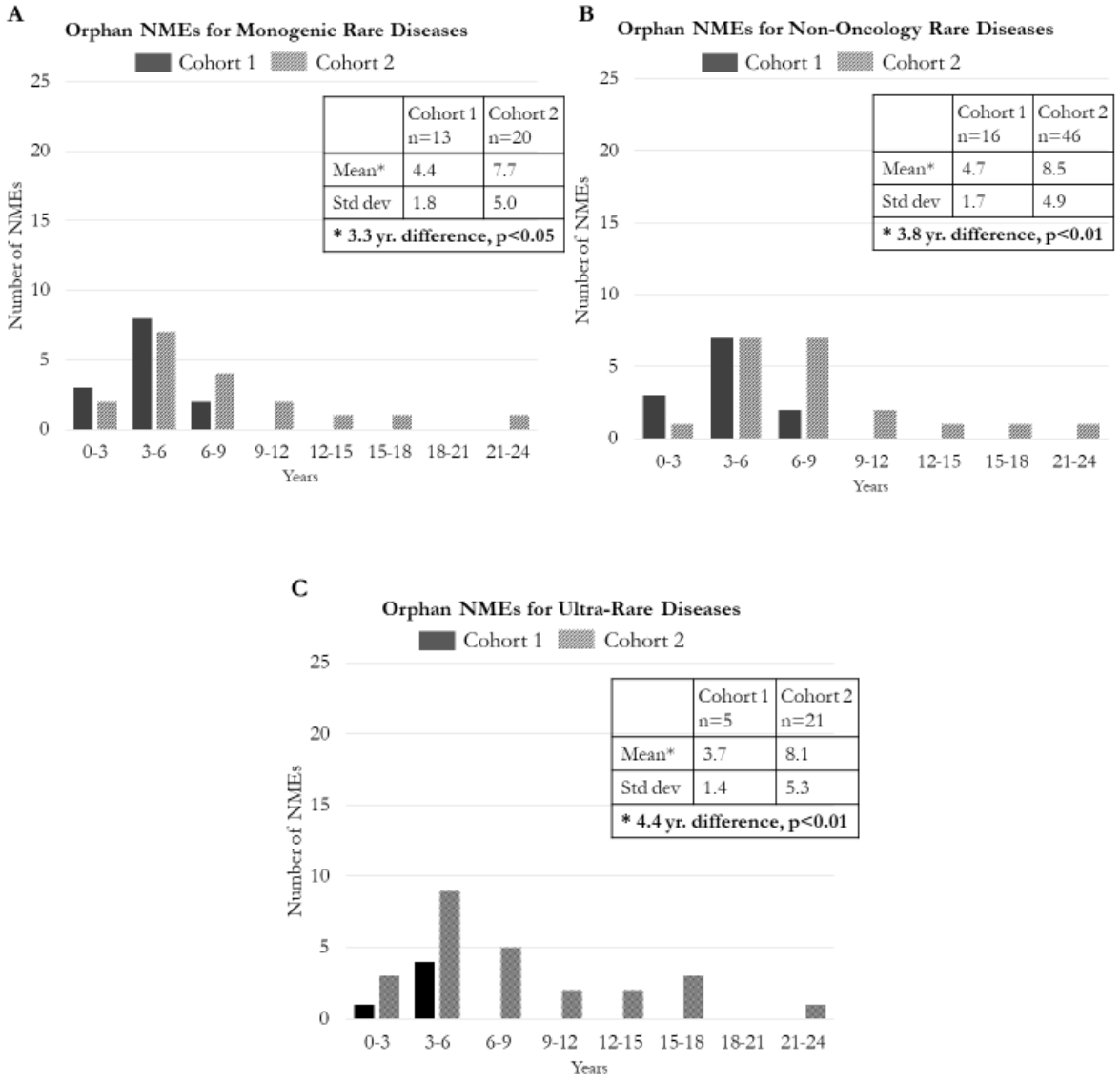


To further understand the underlying mechanisms that may be driving the shorter durations observed in firm-RDF collaborations, I explore differences in the characteristics of drugs assigned to each cohort. First, I rerun the analysis considering only drugs indicated for monogenic disease, which are conditions characterized by a single disease-causing genetic mutation, because patient recruitment for these trials may be easier than polygenic disease where identification of patients with a particular mutation can prove challenging (Figure 2.4, Panel A). I then consider only the drugs approved for non-oncology indications because oncology trials are often considered more complex in design (Panel B) and only the drugs approved for orphan diseases that qualify as "ultra-rare" where recruitment is expected to be more difficult (Panel C). In all of these sub-analyzes, the average differences between clinical durations for Cohort 1 and Cohort 2 drugs persist and remain statistically significant. Most notably, when considering only monogenic, only non-oncology, or only

[55] Though specific reasons for longer than average development timelines are usually not reported, I was able to find firm acknowledgment of clinical delays in some FDA filing documents for a few of the drugs in Cohort 2. These included issues related to agreement between the firm and FDA regarding trial design, recruitment challenges, and temporary de-prioritization of the drug's development program by the firm.

the ultra-rare disease drugs, no product developed with RDF collaboration (Cohort 1) spent longer than 5-7 years in clinical development .

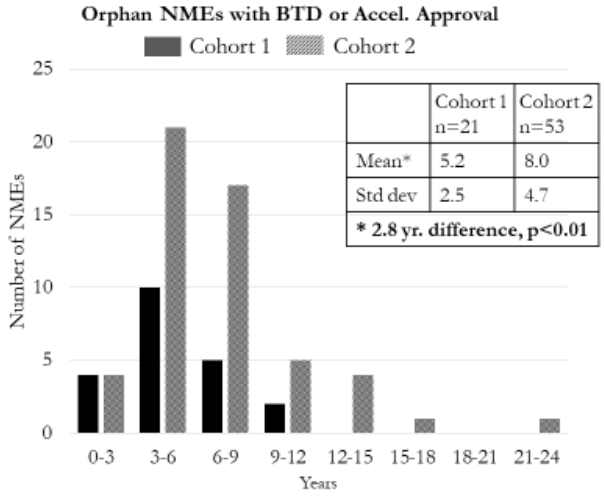
Figure 2.4 Mean Clinical Duration Distributions for Monogenic (Panel A), Non-Oncology (Panel B), and Ultra-Rare (Panel C) Novel Orphan Drugs



Additionally, I rerun the analysis considering only the orphan drugs that qualified for either Breakthrough Therapy Designation or Accelerated Approval, which, in theory, can shorten required clinical development period by allowing for approval based on surrogate endpoints and providing the developing firm with greater access to the FDA for consultations on trial protocols during

development. The findings still persist within this subset of the sample with a mean difference in development duration between Cohort 1 and 2 of 2.8 years (5.2 vs. 8.0 years, $p<0.01$).

Figure 2.5 Distribution of Clinical Durations for Drugs Receiving Breakthrough Therapy Designation or Accelerated Approval



2.5 Discussion

These results are suggestive of the notable role firm-RDF partnerships may play in a novel orphan drug's clinical development duration. The statistically significant difference in average development times between drugs developed with firm-RDF collaboration and drugs developed by firms-only increases when considering various subsets of drugs within each cohort. Comparing the distributions provides insight into potential mechanisms underlying why mean development durations appear shorter for Cohort 1 drugs. In particular, the tighter distributions of Cohort 1 development durations suggest that the benefit of firm-RDF collaboration may lie in avoidance of delays that are common within clinical trials. Cohort 1 drugs rarely seem to spend longer in development than the average development period for all orphan drugs.

The idea that RDFs may help firms avoid common delays in clinical develop is not only supported by data from this analysis but is reinforced by the conceptual framework developed in

Chapter 1 of this dissertation. Rare disease clinical trials are particularly challenged with recruiting enough patients to meet enrollment targets, identifying and validating biomarkers to design the most efficient trial protocol, and determining the most appropriate endpoints to measure based on the natural progression of the disease. The innovative way that RDFs are engaging in the disease research ecosystem directly attempts to address these challenges through the creation of data-driven patient registries, establishment of clinical trial networks already set up to study the disease, and generation of biomarker and natural history studies.

Further, these findings do not suggest that FDA-sanctioned pathways designed to shorten development timelines are driving the average differences in clinical development duration between Cohort 1 & 2 drugs. The statistically significant difference in development durations for firm-RDF collaboration drugs compared to firm-only drugs persists when considering only the drugs that qualified for Breakthrough Therapy Designation or Accelerated Approval. This result suggests that the role of RDFs in helping firms accelerate development timelines is more complex than simply aiding in the procurement of FDA expediated status for rare disease drugs.

In theory, firms could execute research-complementary activities that mitigate risk during clinical development on their own. However, RDFs can undertake these activities more effectively than firms due to their singular strategic focus, close connection with the patient community, and ability to cultivate relationships across various types of disease experts. Compared to biopharma firms, RDFs operate at the center of the patient community and have the ability to more quickly identify and recruit patients with the disease to join a research registry, donate tissue and DNA samples to a biobank, or participate in a natural history study. Because RDFs are entities founded and led by highly motivated patients, they create a sense of common purpose around cure-seeking product development and encourage other patients to share details on their disease state that are important for study recruitment but that they might not otherwise be willing to provide (e.g. their symptoms,

prior treatments, disease subtype). Though biopharma can also create recruitment registries, those developed by RDFs include research-relevant details beyond the typical patient contact and demographic information.

Additionally, RDFs, as mission-driven nonprofits, are more easily able to build connections to the scientific and medical community than biopharma firms. Concerns with patenting and commercialization rights often make cross-sector collaborations challenging, but RDFs are not motivated by patenting, publishing, or generating revenue. Instead, RDFs operate under a single, cure-seeking mission which allows them to form collaborations with scientists and clinicians from across sectors. These relationships are critical, particularly in rare diseases, for the formation of clinical trial networks and execution of disease-specific studies that inform clinical trial protocols (e.g., natural history and biomarker studies).

Finally, acquisition of deep disease expertise and execution of disease-specific research activities takes significant time and resources, and though biopharma firms also have the ability to make this investment for the diseases where they intend to pursue product development, it may not be economically rationale. The investment incentive is higher for RDFs because they are singularly focused on cure finding for one particular disease. This means that RDFs can apply their disease expertise across multiple projects, which is unlikely to be the case for biopharma firms pursuing development across diseases.

These findings send an important signal to drug developers considering clinical programs in rare disease: seek collaborations with patient-led foundations when possible. Collaborations can take many forms, such as formal venture philanthropy investment or informal resource sharing, but the underlying goal of an RDF is to alleviate obstacles to drug development in their disease. Firms should find a way to take advantage of the opportunities RDFs create for their benefit.

2.5.1 Limitations and Opportunities for Future Research

This analysis has several limitations. Notably, the sample size is modest, which precludes the use of more robust empirical tests and models beyond difference in means tests. However, the small sample size reflects the very recent nature of the phenomenon and its nascency: the first novel rare disease drug developed with firm-RDF collaboration was approved in 2012, and of the 28 total drugs that have come to market with the active involvement of RDFs since that point, 12 were approved as recently as 2020. Further, more than 15 drug candidates currently undergoing clinical development (not yet approved) appear likely to be supported by both firms and RDFs.[56]

Additional limitations related to the timing of data disclosure restrict the scope of this analysis. First, because regulatory dates are not disclosed by the FDA until after drug approval and firm-RDF partnerships are not widely publicized until the later stages of drug commercialization, I can only measure clinical development durations retrospectively for drugs that have already received approval. This fact precludes the inclusion of unsuccessful drug development programs (e.g., drugs where development was terminated after earlier phased trials due to either scientific or commercial feasibility concerns). Second, the lack of consistent disclosure around preclinical studies associated with a particular drug candidate limits the ability to accurately measure the length of time a drug spent in research before entering the clinical development period. Therefore, I cannot observe research activities commencing prior to IND filing. Future research should consider different outcomes measures and study designs that work around data availability limitations in attempt to quantify likelihood of success given RDF collaboration and measure the entire R&D period (including preclinical phases) for new products.

[56] Firm-RDF collaborations for development-stage drugs are speculative based on information released by the RDF but have not been confirmed by the firm or the FDA. Additionally, it is unlikely that all of these drugs in development will receive FDA approval.

Finally, future research should use qualitative study designs to more accurately pinpoint specific mechanisms driving the shorter clinical durations for firm-RDF collaboration drugs. Informal interviews conducted for this work suggest that a survey of firm managers who participated in successful firm-RDF collaborations could help identify the components of partnership that were most beneficial during the clinical development process from the perspective of firms (e.g., patient registries, access to disease experts, access to clinical sites, etc.).

2.6 Conclusion

This work documents shorter average clinical development durations for novel, orphan drugs developed under firm-RDF collaboration compared to novel, orphan drugs developed by firms only. Firm-RDF collaboration drugs rarely spent longer in clinical development than the industry average, whereas this was a common occurrence for drugs that were developed by firms only. Collaboration drugs appear to almost entirely avoid an abnormally long development process, a costly, undesirable outcome for firms. This finding, coupled with analysis presented in prior work (Chapter 1), provides evidence that the value of firm-RDF collaboration may be in mitigating common challenges that arise during clinical testing, such as participant recruitment, site identification and set-up, trial protocol design, and endpoint selection. While firms can successfully undertake research activities that aid in clinical development on their own, partnering with an RDF offers economic advantages as RDFs can more effectively execute many of these disease-specific initiatives due to their ability to form strong relationships with the critical stakeholders across industry and non-industry sectors. Firms pursuing product development in rare diseases should proactively identify opportunities collaborate with RDFs prior to the start of clinical testing.

Chapter 3 The Use of Digital Health Technologies in Clinical Research: Notable Differences for Product Development Firms

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Abstract

A popular topic in the recent medical policy literature, the use of digital health technologies (DHTs) in clinical trials has grown rapidly over the last two decades, and regulators have recently issued a series of guidance documents to further encourage appropriate, evidence-based adoption. Noting that recent growth appears attributable entirely to increased DHT use in trials sponsored by non-biopharmaceutical entities, such as academic medical centers, rather than by biopharmaceutical firms, we compared DHT usage by sponsor type to document observable differences in trial characteristics. We found clear evidence that when biopharma sponsored trials did use a DHT, the trials were more likely to be designated for regulatory review and study therapeutically addressable diseases rather than behavioral conditions, which is consistent with biopharma firms' pursuit of product development. Further, biopharma sponsors were more likely to use conventional, sensor-enabled hardware (e.g., Holter monitors) rather than newer, software-enabled DHTs that may lack regulatory precedent (e.g. social media, mHealth apps). Recognition of these differences in DHT use by sponsor type could help regulators issue guidance that more specifically outlines best practices for DHT adoption in product development trials where biopharma firms may be hesitant given the regulatory risk.

3.1 Introduction

The use of digital health technologies (DHTs) in clinical research is a popular, emerging topic in the medical policy and regulatory science literature. Several consortiums of academic researchers and industry stakeholders have recently formed to better understand the potential benefits of these tools for the conduct of clinical trials, which may include richer data collection and more inclusive trial designs enabled by remote patient monitoring. The Food & Drug Administration (FDA) has also launched several initiatives to encourage the appropriate, evidence-based adoption of DHTs in clinical trials, including issuance of a series of draft guidance documents intended to advise trial sponsors.[57]

In our previous work, we documented and categorized the various ways in which DHTs have been used in trials and quantified the substantial growth of these technologies over the most recent two decades (Marra et al. 2020). In 2018, more than 1,900 new clinical trials used a DHT, and since the year 2000, growth in DHT use has been estimated at 32% CAGR (See Appendix C.1, Figure C.1.1).[58] In subsequent analysis of DHT usage, we noted that the majority of recent growth has not been driven by biopharmaceutical firm use of these tools but is instead attributable to increased use by non-biopharma trial sponsors, such as academic medical centers, hospitals, and government research entities. [59,60] We hypothesized that the relatively low adoption of DHTs among firms may be driven by underlying differences in the objectives of biopharma and non-biopharma sponsors in

[57] The most recent FDA draft guidance document was issued in December 2021

[58] In Marra et al. 2020, the estimated CAGR was 34% from 2000-2017. In this paper, we update the data and find a 32% CAGR from 2000-2018.

[59] For example, from May 2019-Feb 2021, 8-9% of all newly started industry funded trials used a DHT. Whereas over the same period, 16-18% of all newly started non-industry funded trials used a DHT (Marra et al. 2021)

[60] "Non-biopharma sponsors" are defined as any entity other than a for profit biopharmaceutical firm, including academic centers, scientists, government affiliated institutions, and for profit labs and research institutions.

conducting clinical trials. Specifically, firms tend to conduct trials for product development purposes whereas other entities execute trials for a broader range of objectives, such as scientific advancement or clinical practice innovation. [61]

Therefore, in this study, we asked whether notable differences could be observed in how biopharma sponsors have used DHTs compared to non-biopharma sponsors. Starting with the comprehensive set of clinical trial records for the last two decades, we used a text search algorithm to identify trials where a DHT was used and flagged when a biopharma firm was listed as the primary sponsor. Any trial with a sponsoring entity not categorized as a biopharmaceutical firm was labelled "non-biopharma sponsored". Comparing biopharma sponsored DHT trials to non-biopharma sponsored DHT trials, we analyzed relevant trial characteristics, such as the regulatory status of the trial, the condition being studied, and the type of DHT that was used. We then manually reviewed the 176 biopharma sponsored DHT trials that were launched over a recent five-year period (2015-2019) to classify the primary purpose of the DHT within the trial (e.g., as the health intervention itself, as a data collection instrument, or for verification of the DHTs function) (See Appendix C.1, Figure C.1.2 for detailed explanation of use cases described in Marra et al. 2020).

Our results confirm that when biopharma firms use a DHT, the trials are frequently designated for regulatory review (phase 1-3) and target therapeutically addressable diseases, which is consistent with biopharma firms' pursuit of product development. Additionally, firms tend to rely primarily on conventional, sensor-enabled hardware DHTs to collect endpoint data (e.g., Holter monitors, continuous glucose meters). Conversely, non-biopharma DHT trials are exploratory or evidence generating (rarely designated for regulatory review), more likely to target lifestyle and behavioral

[61] Clinical trials intended only for publication (not for regulatory review) are captured in this analysis because as of September 2007, the International Committee of Medical Journal Editors requires researchers to publicly register trials *before* publication of the study in any of its member journals.

conditions (e.g., physical activity, smoking), and frequently rely on newer, software-enabled technologies that run on general computing platforms and may not have regulatory precedent (e.g., social media, virtual reality).

These findings are relevant for regulators as they seek opportunities to encourage the appropriate and evidence-based adoption of DHTs. To date, FDA issued guidance for how to include DHTs in trials has been primarily suggestive and addresses "trial sponsors" generally. In particular, the guidance seems to stop short of recognizing the specific objectives of biopharma firms conducting clinical trials – namely product development rather than scientific publication and/or clinical practice innovation. To support and encourage the appropriate adoption of technology within product development trials, the FDA should consider issuing guidance that increases firm confidence in regulatory acceptance of DHT use in trials. For example, the FDA could publish a list of specific DHTs that have been validated for endpoint collection by disease or establish a new voluntary pathway for firms to seek assurance that a particular digitally collected endpoint will be acceptable in regulatory submissions prior to commencement of the trial.

3.2 Background

3.2.1 Digital Health Technology Definition

The FDA has preliminarily defined a digital health technology (DHT) as "a system that uses computing platforms, connectivity, software, and/or sensors, for healthcare and related uses" (Draft FDA Guidance, Dec. 2021). Examples include mobile devices, mobile apps, senor-based monitoring tools, and online social platforms, among others (National Academies Report 2019). According to the FDA, a DHT can consist of hardware, software, or a combination of both hardware and software components. For example, a sensor-based activity tracker used to measure step count is a hardware-enabled DHT. Alternatively, a smartphone-enabled survey that collects patient-reported

outcomes (PROs) is a software-enabled DHT that runs on general computing platforms. Finally, a continuous glucose monitor that relies on a sensor and connection to a mobile application for data reporting and sharing is a single-purpose DHT that encompass both hardware and software to achieve its desired function.

The FDA's DHT definition and examples provided in the draft guidance document, as well as those outlined in a 2019 National Academies report titled "Virtual Clinical Trials", are nearly identical to those encompassed by the term "connected digital product" developed for our previous work (Marra et al. 2020). A "connected digital product" was defined as an innovative technology that is "software-driven, sensor-based, and patient-focused" and examples included non-invasive wearables, mobile applications, ingestibles, and assessments delivered via mobile platforms. In an effort to achieve unity and clarity in the emerging digital medicine literature, we built on our prior analysis in this article, but, we have chosen to adopt the FDA's terminology and refer to products of interest as "digital health technologies" or "DHTs" to focus on the relevance of our findings for regulatory science and policy.

3.2.2 Potential Benefits of DHT Use in Clinical Trials

DHTs alter traditional data measurement practices by collecting data on participant biometrics, health behaviors and treatment experiences outside of scheduled site visits – a practice called "remote patient monitoring". More frequent, or even continuous, monitoring of participants has the potential to increase both the accuracy and amount of data generated during a clinical study, and research has suggested that the data collected via remote monitoring may offer clearer insight into how patients will ultimately adhere to an investigational treatment once it is approved (e.g., by better approximating a real world, non-controlled setting) (Polhemus et al. 2019).

Notably, the incorporation of DHTs in a clinical study creates the opportunity for (at least partially) virtual trial protocols that are designed in a more decentralized manner. Such "decentralized trials" use DHTs to remotely collect information throughout trial recruitment and study execution, ideally improving the experience for trial participants by reducing the number of times a participant must interact in-person with the trial site (National Academies of Sciences 2019; Apostolaros et al. 2019).[62] Moving toward a decentralized study design that relies on digital technology and increased localization of care is expected to improve the inclusiveness of clinical research – a topic of upmost importance to regulators and the broader medical community (FDA Draft Guidance 2022; National Academies of Sciences 2022). While a fully decentralized clinical trial removes many geographic and demographic related constraints that impede broad participation among patient groups, aspects of remote patient monitoring can also be benefit site-based trials (CTTI 2018).[63] Encouragingly, a few recent studies have shown that such trial designs can broaden access and increase the diversity of participants (Stewart et al. 2022; Hirsch et al. 2017).

If these benefits of DHTs bear out, encouraging the use of DHTs within product development trials could lead to the generation of richer data about investigational drug candidates during clinical testing (phases 1-3 trials). For example, increased quantity, and perhaps quality, of data generated through DHT-enabled continuous monitoring may enhance (either positively or negatively) pre-approval understanding of drug efficacy and safety in the true patient population. In turn, regulators may be able to make more informed approval decisions. Additionally, richer safety and efficacy data about investigational drugs could prove useful for reimbursement and clinical practice adoption

[62] Decentralized trials are defined as those in which some or all study assessments or visits are conducted at locations other than the investigator site via any or all of the following DCT elements: tele-visits; mobile or local healthcare providers, including local labs and imaging centers; and home delivery of investigational products (CTTI Digital Health Trials 2022)

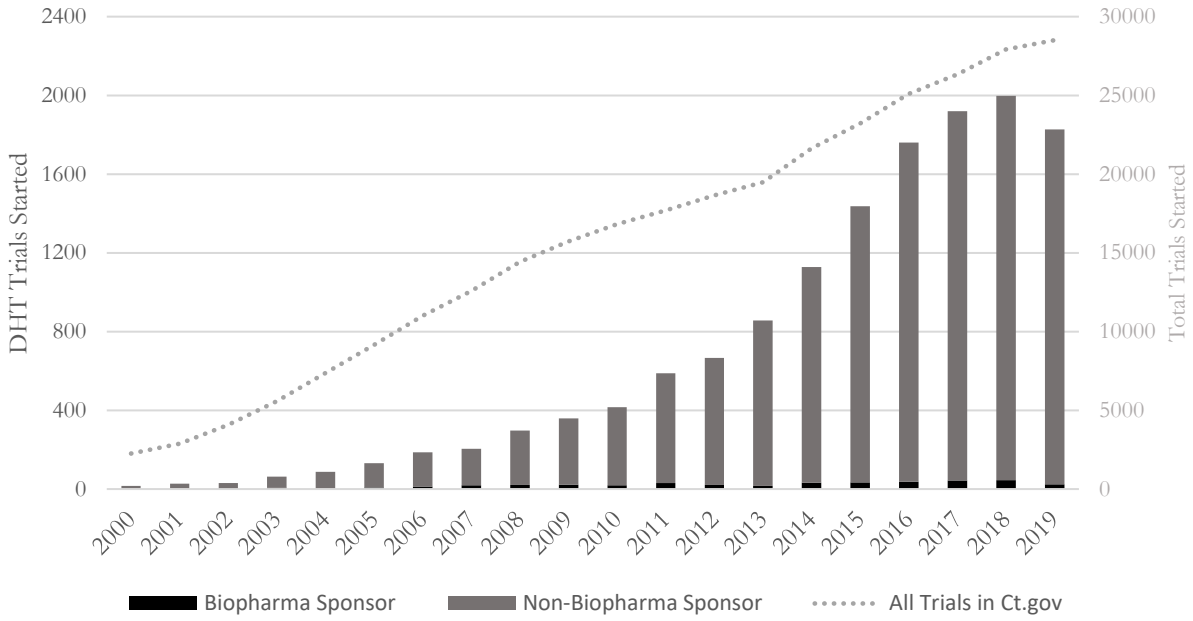
[63] Indeed, decentralized trials to not need to be completely virtual and most trials that incorporate DHTs are neither fully remote nor fully site-based (CTTI 2018; Apostolaros et al. 2019).

decisions after the product approved. For example, evidence generated from late-stage (pivotal) regulatory trials has increasingly been used by payers and clinicians as justification for limiting initial coverage and prescribing practices (Chambers et al. 2021; Werth 2013).

3.2.3 Growth in Clinical Trials Using DHTs Over Time

The number of clinical trials started annually that use a DHT has grown substantially over recent decades (Marra et al. 2020; Sharma et al. 2018). We replicated recent analysis as part of this study and reaffirmed this trend, documenting a 32% CAGR in DHT usage over a recent 19-year period (2000-2018).[64] In the early 2000's, less than 100 trials started each year included a DHT, whereas since 2016, more than 1,500 trials were started annually that use a DHT.

Figure 3.1 Growth in Clinical Trials Using DHTs Over Time



Notes: 1. This figure replicates the analysis published in Marra et al. 2020 and incorporates two additional years of trial data. Trials are classified by their start date as reported in the trial record and the sponsor type is classified by the authors based on the entity name listed in the "sponsor" field. 2. The decline in DHT trial starts observed in 2019, may be due to a delay in registration by trial sponsors.

[64] CAGR is the compound annual growth rate calculated from 2000-2018. Our previous work found a 34% CAGR from 2000-2017 (Marra et al. 2020).

3.2.4 DHT Use Cases for Clinical Trials

DHTs have been used in a variety of ways in clinical trials. In prior work, we reviewed hundreds of clinical trial records to determine the most common ways that trial sponsors incorporate DHTs and found that a trial may: 1) validate or verify the DHT's functionality, 2) use the DHT to capture endpoint data for another intervention (such as a drug/drug candidate), or 3) test the DHT as an intervention itself (Marra et al. 2020).[65] Additionally, with the recent increase in virtual consultation and telehealth delivery, some clinical trials use DHTs to support virtual check-ins with site investigators. For example, smartphone-enabled teleconsultations (via Zoom or other similar platforms) have been used in trials to allow participants to remotely interact with site coordinators to administer PRO instruments or clinical outcome assessments.[66]

3.2.5 Barriers to DHT Adoption Among Biopharma Trial Sponsors

Despite growth in DHT usage and recognition of several unique ways in which DHTs can be incorporated into trials, trial sponsors still face barriers limiting more widespread adoption of DHTs in trial protocols. For example, technical and implementation-related challenges when using a DHT are quite common and can include concerns protecting patient privacy and security, training patients to use the technology, providing technical support, and financially covering the cost of these tools (National Academies Report 2019; Polhemus et al. 2019; Coert et al 2021; Kadakia et al 2021). Even basic trial operations, such as electronically collecting patient consent and signatures, have proven difficult for many sponsors (Hirsch et al 2017).

[65] In the original classification of connected product use cases used in Marra et al. 2020, testing the technology's clinical usability was described as a separate category. For this analysis, usability testing has been folded into verification and validation category.

[66] When a DHT is used to facilitate communication between participant and trial investigators the DHT is classified as being used for endpoint data collection.

Biopharma sponsors, in particular, face added barriers to adoption driven by the inherent regulatory risk associated with product development trials. In general, research has shown that biopharmaceutical firms often have risk averse cultures when it comes to new product development that may slow technology adoption (Polhemus et al. 2019). Additionally, because of the high cost and lengthy timelines associated with clinical research, biopharma firms require clear and specific guidance from regulators before altering traditional trial protocols, as would be required to incorporate a DHT (Coert et al. 2021).

3.3 Methods

We downloaded the complete set of clinical trial records available from the ClinicalTrials.gov database in December 2021.[67] We limited the sample of clinical trials to those launched from 2000 to 2019, inclusive, where the current trial status indicated that the trial had formally launched (i.e., it had at least begun to recruit participants).[68] Trials with start dates in 2020 were excluded because the onset of the COVID-19 pandemic disrupted clinical research plans and led to clinical trial registration delays.

To identify DHTs, we supplemented the branded product search term list used in Marra et al. 2020 with additional general terminology indicative of the use of a DHT (e.g., "mobile app").[69] The resulting list included 1137 search terms (for a full list of search terms used see Appendix C.2).

[67] ClinicalTrials.gov is a publicly-available resource provided by the United States (US) National Library of Medicine and includes over 312,000 research studies in the US and abroad. Since September 2007, the party or parties responsible for a clinical trial have been required to register on ClinicalTrials.gov when that trial is being used to support the regulatory approval of a new therapeutic product (e.g., a drug or medical device), and the International Committee of Medical Journal Editors requires *ex ante* trial registration in order to publish studies in any of its member journals.

[68] Trials with status of "Withdrawn" or "Not yet enrolling" were excluded from the analysis because these designations indicate that while planned, the trial had not yet launched at the time of data collection.

[69] In Marra et. al 2020, product lists sourced from the Atlas by Human First, CTTI Mobile Technologies Database, Frost and Sullivan's 2016 Wearable Technologies Report, and Scripps Research Digital Health Library were collated to extract a comprehensive list of products' model names and manufacturers. Since clinical trial details are entered manually by trial sponsors, the research team read a subset of trials to identify how investigators most commonly referred to products.

Using the search term list, we performed an automated text search within the downloaded trial records. We used a comprehensive search algorithm, which allowed us to capture text in all relevant database fields in which the use of a DHT might be recorded (e.g., outcome measures, intervention).

To identify trial sponsor type, we searched within the "sponsors" field in the clinical trial record for the names of biopharmaceutical firms. In cases where the sponsor name was ambiguous, we searched for the organization's website to confirm whether the entity was an industry firm engaged primarily in pharmaceutical or biotechnology product development. Trials where a firm name was found in the sponsor field were designated as "biopharma sponsored" and the remaining trials were designated as "non-biopharma sponsored".[70] The trial phase, study type, and conditions were pulled from structured data fields (with options for multiple entries) in the trial record.

We analyzed differences between the biopharma sponsored and the non-biopharma sponsored DHT trials based on factors such as the frequency of DHT use, the type of DHT used, and the medical conditions in which DHT use was most common. We used a compound annual growth rate calculation to quantify the increase in DHT use over time and when possible, we performed statistical comparisons using two-sided difference in means tests.

To more specifically document the use of DHTs by biopharma firms, we manually reviewed biopharma sponsored trials with start dates in the most recent five years of data (2015-2019, inclusive). We categorized each trial based on the primary purpose of the DHT in the study: 1) validation and/or verification of the DHT, 2) using the DHT as the intervention, and 3) using the DHT to collect endpoint data for another intervention.[71,72]

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[70] Non-biopharma sponsored trials are led by hospitals, academic medical centers, government, nonprofits, and other industry related organizations not engaged in product development.

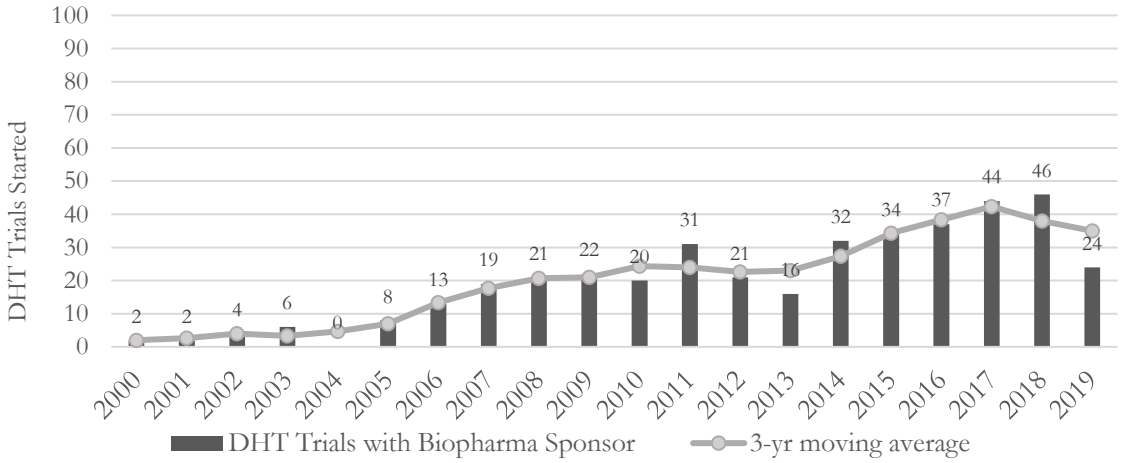
[71] These use case categories were previously defined in Marra et al. 2020.

[72] We also read the trial to assess whether or not the sponsor planned to submit it for regulatory. This process was straightforward for trials designated as defined phases (1-4). However, because trials testing a medical device do not follow the same regulatory milestones as investigational drugs, we looked specifically for language indicative of likely

3.4 Results

Biopharma firms sponsor only a small fraction of the total trials using a DHT. For example, less than 50 out of more than 1900 total DHT trials in 2018 had a biopharma firm as a sponsor. However, the number of biopharma sponsored DHT trials has grown slowly and steadily over time, particularly in recent years. Between 2015 and 2019, on average 37 new trials using a DHT were started annually by biopharma firm sponsors, compared with 24 on average annually between 2010-2014 and 17 on average annually between 2005-2009.

Figure 3.2 Annual Number of DHT Trials Started with Biopharma Sponsors



Notes: 1. Trials are classified by their start date and sponsor type as reported in the ClinicalTrials.gov record. A 3-year moving average of the annual DHT trial starts is also depicted as most clinical trials are in progress for longer than the year in which the study commences. 2. The decline in biopharma-led DHT trial starts observed in the most recent year of data, 2019, may be due to a delay in registration by trial sponsors.

We observed differences in how biopharma sponsors used DHTs compared to non-biopharma sponsors. First, biopharma firms were more likely to use sensor-enabled hardware DHTs (e.g. Holter monitors, biosensors, and continuous glucose monitors) whereas non-biopharma sponsors were more likely to use DHTs that include software applications that run on general-purpose computing platforms (e.g., mobile apps, mhealth, virtual reality and social media platforms). The use

regulatory submission in the device trials, such as the phrases "feasibility study" and "pivotal trial". Biopharma sponsored trials testing a medical device comprised a small minority of the sample.

of smartphones, various types of activity monitors, wearables and the internet-enabled tools was common across trials sponsored by both biopharma and non-biopharma organizations.

Table 3.1 Most Commonly Used DHTs Across Recent Biopharma & Non-Biopharma Sponsored Clinical Trials (2015-2019)

	Biopharma Sponsored (n=176)		Non-Biopharma Sponsored (n=8,533)	
Rank	**DHT Used**	**No. Trials**	**DHT Used**	**No. Trials**
1	Holter monitor	25 (14%)	smartphone	1504 (18%)
2	wearable	25 (14%)	internet	1088 (13%)
3	smartphone	21 (12%)	mobile app	957 (11%)
4	freestyle libre	14 (8%)	text message	657 (8%)
5	online survey/questionnaire	12 (7%)	wearable	608 (7%)
6	mobile app	11 (6%)	virtual reality	558 (7%)
7	activity monitor	10 (6%)	online survey/questionnaire	483 (6%)
8	actigraph	9 (5%)	activity monitor	477 (6%)
9	biosensor	6 (3%)	telemedicine/telehealth	465 (5%)
10	ipad	6 (3%)	actigraph	465 (5%)
11	accu chek	5 (3%)	redcap	401 (5%)
12	kinesia	4 (2%)	fitbit	372 (4%)
13	omron	4 (2%)	mhealth	337 (4%)
14	internet	4 (2%)	social media	327 (4%)
15	remote monitoring	4 (2%)	ipad	279 (3%)

Note: Trial counts include the number of trials started between 2015-2019 (inclusive) where sponsors indicated the noted DHT was used. Some trials use more than one DHT so percentages are not expected to sum to 100%.
Source: Authors analysis of ClinicalTrials.gov records

Notably, we find that biopharma sponsored DHT trials were more likely to be registered as Phase 1-4, which aligns with biopharma firms' product development objectives. Conversely, non-biopharma DHT trials were typically not phased, suggesting that a higher percentage of the biopharma DHT trials were intended for regulatory submission: 64% of biopharma DHT trials were designated with a regulatory phase compared to 11% of non-biopharma DHT trials ($p<0.001$). The spilt between interventional and observational studies was relatively similar for biopharma and non-biopharma sponsored trials, with the majority of trials being interventional in both cases.

Table 3.2 DHT Trial Characteristics (2000-2019 Start Dates)

	Biopharma Sponsored (n=402)	Non-Biopharma Sponsored (n=13,599)
Study Type		
Interventional	312 (78%)	11,258 (83%)
Observational	90 (22%)	2,341 (17%)
Phase		
Not Designated	146 (36%)	12,147 (89%)
Phase 1	83 (21%)	273 (2%)
Phase 2	78 (19%)	484 (4%)
Phase 3	55 (14%)	238 (2%)
Phase 4	40 (10%)	357 (3%)

Notes: 1.The table includes all trials using a DHT with start dates between 2000-2019, inclusive. 2. Phase 1 / 2 trials are grouped with Phase 2; Phase 2 / 3 trials grouped with Phase 3. "Not designated" indicates the studies are likely exploratory or not intended for regulatory submission because the trial sponsor either did not select a phase or indicated that a phase was not applicable.

Source: Authors' analysis of ClinicalTrials.gov records.

Additionally, as expected, biopharma firms were most likely to use DHT for trials in therapeutically-addressable conditions, such as diabetes, cardiovascular diseases, COPD, cancers, and mental health disorders. DHT trials sponsored by non-biopharma entities also target the same large market conditions but were much more likely to study lifestyle behaviors, such as physical activity, smoking, sleep, drug and alcohol abuse, and diet and nutrition.

Table 3.3 Most Common Conditions Studied in DHT Trials

Rank	Biopharma Sponsored	No. Trials (n= 402)	Non-Biopharma Sponsored	No. Trials (n=13,599)
1	Diabetes	68 (17%)	Cardiovascular Disease	2304 (17%)
2	Cardiovascular Disease	59 (15%)	Mental Health Disorder	2226 (16%)
3	COPD / Asthma	54 (13%)	Cancer (any type)	1947 (14%)
4	Cancer (any type)	36 (9%)	Diabetes	1751 (13%)
5	Mental Health Disorder	31 (8%)	Obesity	1307 (10%)
6	Rare Disease (any)	27 (7%)	Pain	1191 (9%)
7	Alzheimer Disease	15 (4%)	Physical Activity	925 (7%)
8	Atrial Fibrillation	14 (3%)	Smoking	746 (5%)
9	Pain	11 (3%)	Sleep Disorder	700 (5%)
10	Macular Degeneration	9 (2%)	Substance Abuse	633 (5%)
11	Parkinson's Disease	8 (2%)	COPD / Asthma	598 (4%)
12	Obesity	8 (2%)	HIV/AIDS	496 (4%)
13	Sleep Disorder	7 (2%)	Diet & Nutrition	333 (2%)
14	Solid Tumors	6 (1%)	Dementia (incl. Alzheimer)	317 (2%)
15	Urological Disorder	6 (1%)	Pregnancy / Postpartum	281 (2%)

Notes: 1. Ranking is based on the number of times each condition was reported. Trials can include more than one condition so percentages reported may not add to 100%. 2. Condition definitions: cardiovascular disease broadly includes heart failure, stroke, coronary artery, hypertension, etc. Mental health disorders include bipolar, depression, schizophrenia, autism, anxiety disorder, etc. Rare disease includes conditions listed in the National Organization for Rare Disease database. Atrial Fibrillation includes arrythmia. Source: Authors' analysis of trial records.

3.4.1 Sub-analysis of Recently Started Biopharma Sponsored DHT Trials

In the second part of this analysis, we conducted a manual review of all recently started biopharma sponsored clinical studies: 176 trials in total with start dates between 2015-2019, inclusive. We found that in the majority of these trials (59%, n=104), the primary purpose of the DHT was to collect endpoint related data in a trial testing another intervention (e.g., an investigational drug). In approximately 30% (n=52) of the biopharma sponsored studies, the DHT was the primary intervention being tested. The remaining trials were feasibility studies aimed at generating validation, verification, and/or usability data (14%, n=24). There were four studies where more than one DHT was used and the primary purpose for each was different.[73] Table 3.4 presents examples of trials from our sample, classified by their DHT use case.

[73] For example, in NCT02347761 two DHTs were used for different purposes: an eFlow nebulizer device was included as part of the intervention (to deliver an experimental drug) and a Holter monitor was used to collect endpoint data. In these four trials, the trial was categorized according to *all* relevant use cases, which is why the percentages of trials for each use case sum to more than 100%.

Table 3.4 Selected Examples of Biopharma Sponsored Clinical Trials Using Digital Health Technologies (DHTs)

NCT ID	Sponsor	DHT	Use	Study Description
02497937	GlaxoSmith-Kline	Body Guardian	Collect secondary endpoint data	Phase 2 randomized trial to assess efficacy of investigational drug vs. placebo in respiratory function for patients with heart failure. Respiratory rate is measured continuously over time by BodyGuardian sensor.
03569631	Tetra Therapeutics	iPad-based cognitive tests	Collect other endpoint data	Phase 2 randomized trial to assess safety and efficacy of investigational drug vs. placebo on cognitive behavior and function in patients with Fragile X Syndrome. NIH Toolbox Cognitive Battery for Intellectual Disabilities tests are administered on iPads.
03559088	Eli Lilly	Smartpho ne-based migraine app	Intervention	Interventional trial to assess whether use of a smartphone app that records migraine burden in the patient's EHR impacts provider actions (e.g., prescribing, referrals) and number of patient medical visits (e.g., clinic, ER)
03936699	Elira Therapeutics	Elira wearable patch system	Intervention	Randomized trial to assess safety and efficacy of the Bluetooth-enabled, Transcutaneous Nerve Stimulator (TENS) Elira wearable patch system in driving weight loss and appetite suppression when coupled with behavioral strategies.
03159546	Abbott Diabetes Care	FreeStyle Libre Flash	Verification /Validation	Multi-center, prospective cohort study to measure accuracy of the FreeStyle Libre glucose monitoring system. Patients with diabetes wear two sensors and test blood glucose levels eight times per day. Results are masked and patients report any device malfunctions.
02875106	Bayer	Wearable, commercial pulse detection systems	Verification /Validation	Study to assess ability of several commercially available pulse detection products (Polar V800, TomTom Runner Heart Rate Monitor, Adidas Micoach Smart Run, etc.) to accurately detect atrial fibrillation or sinus rhythm in diagnosed patients. Standard ECG used as reference.

Source: Author's analysis of ClinicalTrials.gov records.

Finally, our manual review revealed that 64% of the biopharma sponsored trials were likely for regulatory submission, based on inclusion of a trial phase in the registry data. This aligns with expectations in the overall sample based on how many trials were designated as Phase 1-4, which indicate that 64% of biopharma DHT studies were for regulatory submission, as compared with only 11% of non-biopharma DHT studies.

3.5 Discussion

The results of this analysis document observable differences in the use of DHTs in trials sponsored by biopharma firms relative to non-biopharma organizations. First, our study confirms that the vast majority of clinical trials using a DHT over the most recent two decades have been led

by non-biopharma entities (e.g., 1,951 non-biopharma sponsored DHT trials started in 2018 vs. 46 biopharma sponsored). When biopharma firms do incorporate a DHT, the trial is usually intended for regulatory review (64%), which is consistent with biopharma firms' inherent product development objectives. Conversely, only 11% of non-biopharma sponsored DHT trials are designated for regulatory review, suggesting these studies are primarily exploratory or evidence-generating but not product development related and therefore not subject to the same level of regulatory risk.

On a related note, when biopharma firms used a DHT, they were more likely to opt for sensor-enabled, hardware DHTs, such as Holter monitors and continuous glucose meters, whereas non-biopharma sponsors opted for software DHTs that run on general purpose platforms, such as virtual reality, social media, and mHealth applications. This difference may be attributable to different risk tolerances of biopharma vs. non-biopharma sponsors tied ultimately to the trial's intended purpose. For example, many hardware-enabled DHTs have been used in trials for several years and are perhaps considered to be "safer options" from a regulatory perspective, given their precedent, than newer DHTs that rely on general use platforms that have not traditionally been incorporated in clinical trials. Put another way, firms may hesitant to use newer, consumer-focused technologies in product development trials that they plan to submit for regulatory review.

Further consistent with product development objectives, biopharma sponsored DHT trials tended to target medical conditions that are therapeutically addressable, such as chronic obstructive pulmonary disease and rare diseases, whereas non-biopharma sponsors more frequently used DHTs for trials that study lifestyle or health-related behaviors, such as physical activity, smoking, and diet. Therapeutically addressable diseases often have established clinical endpoints that must be measured to assess efficacy of an investigational drug (e.g., HbA1c in diabetes, FEV in lung function, ECG in

heart conditions), and sensor-enabled, hardware DHTs are needed to detect these clinical measures. On the other hand, studies evaluating interventions for lifestyle and behavioral conditions can rely on endpoints assessed by software-enabled products or patient-reported data entry alone, such as activity trackers, eDiaries, and other training or behavioral tracking applications.

Taken together, these findings can inform regulatory guidance documents that aim to encourage the appropriate and evidence-based adoption of DHTs in clinical trials. Since biopharma firms are most likely use DHTs in trials intended for product development, establishing best practices for the use of such tools in regulatory submissions and easing hesitation around technology adoption will be required to grow the use of DHT in these types of clinical trials. In particular, our manual review revealed that biopharma sponsors appear to primarily use DHTs to collect data in a trial testing another intervention (e.g., a drug candidate). Therefore, regulators could produce clear, specific and targeted guidance for how DHT should (and should not) be used in endpoint data collection for new products. This context-specific guidance may be particularly salient in the current environment where the medical and research community has been striving to make clinical trials for new product innovations more diverse and representative of the true patient population.

In practice, issuing guidance around DHT usage specific to the product development context could take many forms but should aim to ease regulatory-related hesitations around technology adoption that firms may possess. For example, the FDA could consider creating and publishing a list of specific DHTs that can be used to collect a particular endpoint within a given disease (e.g., "the Kinesia ONE motor assessment system can be used to measure tremors in patients with Parkinson's disease"). In cases where the DHT does not have any regulatory precedent, the FDA could create a voluntary pathway for firms to submit plans for use of a specific DHT and its associated data collection and receive feedback from the FDA prior to commencement of the trial (e.g., a plan to

use a new mobile app to track changes in mood for patients taking an investigational drug to treat anxiety disorder). A voluntary pathway could serve primarily as an opportunity for firms to start a dialogue with the FDA about incorporation of a DHT before protocol implementation.[74]

3.5.1 Limitations

This work has several limitations. First, reporting the use of a DHT is not a required disclosure in the ClinicalTrails.gov record. Since there are no preset fields that ask sponsors to identify digital technologies, we relied on sponsors entering information about the technology in free text fields. For example, sponsors often indicated a DHT was used when explaining how endpoint data was collected. As a result, the trials identified by our text search algorithm and the totals reported in this study may under-represent the true number of trials that used a DHT. Secondly, although clinical trials must be registered on ClinicalTrials.gov before publication in a medical journal or review by the FDA, sponsors frequently delay registration until some point after trial commencement. This means that trials using DHT that began in the most recent years of our data collection and are currently underway may not yet be reflected in the sample. We attempted to mitigate this risk by considering only trials with start dates through the end of 2019 because we assumed some trials started in the most recent years have yet to be registered.

Finally, this analysis considers only trends in DHT adoption prior to onset of the COVID-19 pandemic (2000-2019), which temporarily disrupted many in-progress trials and may have shifted perspectives and attitudes of trial sponsors around the use of DHTs to enable trials. The long term

[74] Research suggests that these conservations may need to provide firms with assurance that trials will not need to be rerun if the DHT software or hardware is either discontinued or updated during the trial (Stephenson et al. 2020).

effect of the pandemic on the use of technology in clinical research remains an important topic for future research.

3.6 Conclusion

This study built on previous work, which found substantial growth in the use of DHTs in clinical trials overall, to document differences in how biopharma firms use DHTs compared with non-biopharma trial sponsors. Though DHT use among biopharma sponsored trials comprises only a very small fraction of overall DHT use, when biopharma firms do choose to use a DHT, the trials are more likely to be product development related, which is consistent with the inherent objectives of biopharma firms. To encourage the evidence-based and appropriate use of DHTs by biopharma sponsors, the FDA could consider reframing regulatory guidance to specifically address product development studies where firms may be hesitant to use new technology because of regulatory risk.

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Appendices

A: Appendix to Chapter 1

A.1 Research-focused RDF Definition & Examples

To qualify as a research-focused rare disease foundation (RDF), the entity must include therapeutic research and development within their mission. The research efforts must be specific to a single rare disease or group of closely related diseases. The entity must have operations in the United States and be classified as either a private foundation or public charity under the Internal Revenue Service nonprofit tax law, section 501(c)(3) with the most recent Form 990 filing in 2019 or later. This excludes entities that do not have gross receipts of at least $50,000 annually (IRS.gov). Finally, patients and/or their families must have been involved in the initial establishment and ongoing operations of the entity. This last requirement is used to exclude disease foundations formed by academic researchers who are motivated by scientific progress but not necessarily therapeutic development and operate under different timelines than that individuals personally affected by the disease

Table A.1.1 RDF Inclusion Criteria & Examples

RDF Inclusion Criteria		Research geared toward therapeutic dev. part of mission	Focus on single rare disease	501(c)(3) tax exempt status with Form 990 as of 2019	Patient founded
Organization Type	*Example*				
Research-focused RDFs	Rett Syndrome Research Trust	✓	✓	✓	✓
Patient Support Groups	Sick Cells	X	✓	✓	✓
Broad mission medical charities	Bill & Melinda Gates Foundation	✓	X	✓	X
University foundations / nonprofit research institutes	Big Ten Cancer Research Consortium	✓	X	✓	X
Government sponsored foundations	INSIGHT (Int'l Network for Strategic Initiatives in Global HIV Trials)	✓	✓	X	X
Ex-U.S. operating research foundations	Sanfilippo Children's Foundation	✓	✓	X	✓

A.2: Ideal Empirical Experiment & Quantitative Case Study Example

This appendix describes the challenges and limitations in drawing comparisons among rare diseases for the for the purposes of evaluating innovation measures. The experiment is executed in a quantitative case study on the SMA Foundation that required extension manual data manipulation and interpretation.

Ideal Analysis

The ideal analysis would involve closely matching rare diseases with strategic research-active RDFs to similar diseases without research-active RDFs, and observing the effect of RDF establishment on new clinical trial starts within the disease. First, basic information on discreet rare diseases, such as incidence, age of onset, severity, and state of the science (genetic understanding) would be systematically collected, and a matching algorithm would be applied to create a treatment and matched control group. Then, a time series or difference in differences analysis would use the year of RDF establishment (indexed to 0) as the intervention starting point. The difference in the pre-post trend in number of new clinical trial starts for diseases with foundations and their matched controls would be compared. Though in theory this approach seems feasible, in practice, applying this method at scale is problematic. Creation of a matched control group at the disease level is challenging because: 1) given the rare nature of orphan conditions, most are understudied, resulting in a high degree of variability in the availability and accuracy of information by disease, 2) the organizations that do attempt to aggregate rare disease information categorize and name the diseases in a highly inconsistent manner, limiting the ability to compare diseases across data sources without extensive manual interpretation, and 3) metrics that are more difficult to quantify, including level of scientific/genetic understanding within the disease and availability of research funding are essential considerations for evaluating the readiness of the each diseases for the commencement of clinical trial activity.

In the ideal approach, comparisons across diseases could be made using a set of known, quantifiable factors that may impact firm interest in pursuing therapeutic development, such as incidence/prevalence (a proxy for market size), disease severity (a proxy for unmet need and willingness to pay), and age of onset (proxy for length of treatment). However, comparing these seemingly objective measures across diseases can

lead to inaccurate equating of market opportunity and readiness for clinical activity. For example, while a point prevalence estimate could reflect the most accurate measure of potential market size for chronic diseases with mild severity and varying ages of onset, an incidence at birth ("birth prevalence") estimate may be a more accurate representation of market size for genetic, infantile onset diseases where life expectancy is only a few months. Further, the current amount and quality of known information, both across diseases and within each disease itself, is inconsistent. For example, the availability and accuracy of rare disease prevalence and incidence estimates vary widely because established research on the particular condition can be extremely limited. Epidemiological studies, if they exist, tend to focus on specific geographies or populations (e.g. towns in France, people of Ashkenazi Jewish descent) within which the rare disease has been most keenly observed, making systematic extrapolation to the broader potential patient market difficult without further research. Severity and age of onset are also extremely challenging to quantify as these factors tend to vary substantially within the same disease and can be dependent on disease subtype or other patient-specific medical and environmental factors.

Even if these challenges can be overlooked for the purposes of research, accurate comparison of rare diseases across the existing data sources is nearly impossible for a large proportion of the 7,000+ identified rare conditions. The most well established rare disease databases, NORD in the United States and Orphanet in Europe, are useful sources of clinical information for many of the identified conditions, but they do not allow for reliable comparison of non-clinical metrics across diseases. Orphanet, in particular, has undertaken substantial effort to make rare disease information more amendable to research through establishment of consistent data fields, downloadable data files, and creation of a unique identifier. However, completeness and quality of information reported for each disease is highly variable. For example, only 5.5% (379/6,897) of the diseases cataloged in Orphanet have a birth prevalence value reported.

Perhaps presenting an even greater challenge for research is the inconsistent classification of disease names, disease categories, and disease subtypes across rare disease databases. For example, while it may be quite straightforward to identify trials for "Spinal Muscular Atrophy" in clinical trial data from Cortellis, a paid-service database curating detailed therapeutic intelligence data, a search for the same disease name in

Orphanet returns 39 unique identifiers, the names of which suggest various inheritance patterns, clinical manifestations, and subtypes of Spinal Muscular Atrophy. Further complicating matters, each of these 39 disease codes report different estimates for prevalence, age of onset, severity, etc. The challenge in discreetly identifying diseases across datasets makes matching diseases to one another in a convincing manner nearly impossible without rigorous manual evaluation.

Finally, a variety of additional scientific and funding related factors also complicate comparison of clinical trial activity across diseases. Both the level of scientific understanding and the prior investment in basic science research are critical factors that impact a disease's "readiness" for private investment. First, the underlying mechanisms causing rare diseases vary widely in complexity and level of scientific understanding. While 72% of currently known rare diseases are considered genetic, the number of genes involved – and whether or not scientists have identified those genes – can be indicators of eventual therapeutic success. For example, monogenic or single gene causing diseases are generally thought of as easier to target therapeutically, though even within monogenic diseases, the number of different disease-causing mutations can vary. Polygenic rare diseases are quite common, as are multifactorial diseases where a combination of genetic and environmental factors may be implicated in the disease. Scientific understanding of the underlying disease cause, and whether or not the identified cause is responsible for all cases of the diseases or just a portion, can have dramatic implications for comparing diseases that may otherwise appear similar in terms of the more easily quantifiable measures, such as prevalence, age of onset, severity, etc.

Second, disease awareness and relatedly, the availability of public funding can also vary substantially across diseases that are otherwise similar in terms of known quantifiable measures. Differences in public funding and awareness are important to consider as they may also impact a disease's readiness for clinical activity. For example, since 1985 the NIH has provided more than $2.6B for projects related to amyotrophic lateral sclerosis (ALS) whereas projects related to Castleman disease, which has the same incidence, disease severity, and average age of onset, received only $42M in funding over the same time period (NIH RePorter). Unsurprisingly, there have been nearly 1000 new clinical trial starts for ALS and less than 25 for Castleman (Cortellis). Public funding is often used to support basic science and early stage research into disease

understanding and target identification, steps that necessarily need to occur before commencement of therapeutic trials.

SMA Case Study – Additional Details

Given the numerous limitations associated with matching rare diseases at scale to evaluate RDF effect on new clinical activity, a case study approach is one method for comparing diseases in a reliable manner. Existing datasets, such as Orphanet, are still too limited in data completeness, consistency, and quality to be used for this purpose and manual collection and classification of all the critical data points needed to accurately match among the 7,000+ rare diseases is infeasible.

To illustrate the effect of strategic research RDFs on innovative activity within their disease, I start by selecting a disease with clearly established and validated characteristics that can be used to match to other rare diseases with similar validated characteristics. The condition, Spinal Muscular Atrophy (SMA), is one of the more common severe, monogenic, infantile-onset conditions. I select SMA for this analysis for several reasons: first, data tends to be more accurately reported for severe, monogenic conditions affecting children which is critical for insuring accurate matches to comparison diseases and second, I have access to the SMA Foundation (SMAF) leadership team for interviews and internal documents, which enables me to add qualitative richness to the case study.

Starting with data that is available from the rare disease database, Orphanet, I generate several lists of "potential" comparison diseases, matching separately on birth prevalence, age of onset, and monogenic properties. I manually fill in missing or inconsistent data with extensive literature reviews of epidemiological analysis, genetic studies, and clinical reports to narrow down the set of possible matches. I then incorporate historical NIH funding data from the NIH RePorter tool and historical clinical trial activity from the Cortellis database. I consider the "historical" time period to be the "pre-period" for analysis purposes and calculate this period from the year that scientists first identified the genetic cause of the disease to the year the foundation was formed as a nonprofit entity pursuing missions related to therapeutic development. This process allows me to identify the six closest disease matches based on known scientific and publicly available

data. Though the diseases may still differ on unobservable measures, the extensive combination of data sources alongside rigorous manual evaluation ensures that the disease matches are as similar as possible on the primary characteristics likely to impact innovative activity prior to establishment of the RDF.

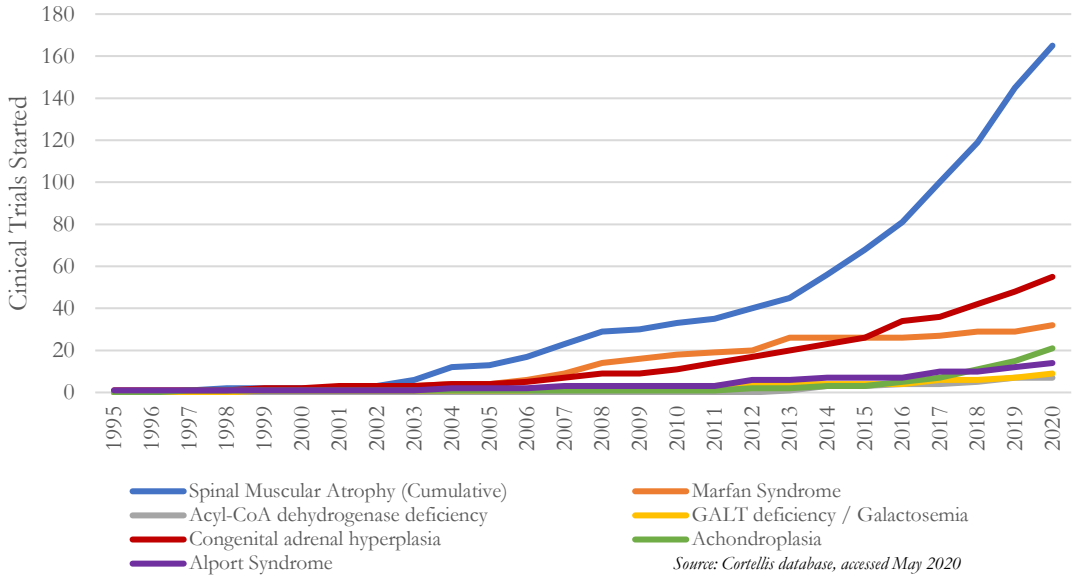
Disease background

Spinal Muscular Atrophy is a devastating monogenic disease affecting an estimated 1 in 11,000 live births, making it one of the most common infantile onset genetic conditions (smafoundation.org). Despite the relatively high incidence for a rare disease and scientific identification of the genetic cause in 1995, NIH funding and clinical trial activity remained stable and low until 2003, when The Spinal Muscular Atrophy Foundation was formed. The Foundation was created by a highly motivated, well-resourced patient family with the explicit mission of enabling and accelerating therapeutic development.

In the years between identification of the genetic cause and the founding of the SMA Foundation (1995-2002), the NIH had funded $18M total in projects related to the disease and only 3 clinical trials had been started. Data from Orphanet and the NIH Reporter tool, supplemented with manual literature reviews and data validation, identified six diseases as the closest matches to Spinal Muscular Atrophy. These comparison diseases have all been identified as monogenic, affect nearly the same number of births in the United States (between 250-750 annually), appear first in infancy or early childhood, and cause debilitating physical, mental, and/or psychological symptoms that markedly shorten lifespan. Further, NIH funding over the eight year period from gene implication in the disease until the formation of the SMA Foundation was relatively consistent across the diseases (between $13-25M) and the number of clinical trials started per disease ranged from 0-3 [See Table 1.2 for details on SMA and the matched controls].

In the years following the formation of the SMA Foundation in 2003, the number of clinical trials started in the disease began to diverge from that of the control diseases. By 2020, a total of 165 trials had been started in SMA whereas on average only 23 had been started in the control diseases (range 9-55).

Figure A.2.1: Cumulative Clinical Trials Started in SMA & Comparison Diseases



A time series analysis anchored around 2003 finds that before 2003, there was no statistically significant difference in the level (_z, *p=0.86*) or slope (_z_t, *p=0.47*) of clinical trials started between SMA and the control diseases (as expected). This suggests that the control diseases are good comparators for SMA in terms of clinical trial activity (absolute level and trends) in the preintervention period. During the first year of the intervention (formation of the SMAF in 2003), there is no statistically significant treatment effect (_z_x9, *p=0.489*), which is also expected as clinical trial starts resulting from foundation-related activity would not be expected for several years. Notably, over time, there is a statistically significant annual increase in the pre-post trend for trial starts in SMA compared to control diseases (_z_x_t9, *p=0.00*). Additionally, we see from the post-trend output that the treatment group (SMA) increased annual clinical trials started in the postintervention period by 1.2, the control group increased annual trial starts over the same period by only 0.13.

Table A.2.1 Interrupted Time Series Regression Output

VARIABLES	ITS Model Annual Trials Started
Initial Mean Level Difference (_z)	0.056
	(0.306)
Difference in Baseline Slope (_z_t)	0.050
	(0.067)
First Year (Level) Treatment Effect (_z_x9)	-1.626
	(2.329)
Treatment Effect on Trend (_z_x_t9)	1.005**
	(0.256)
Constant	0.194**
	(0.070)
Standard errors in parentheses	
** p<0.01, * p<0.05, + p<0.1	

	Post Trend Analysis
Change in Annual Trial Starts in SMA	1.189**
	(0.238)
Change in Annual Trial Starts in Control Diseases	0.135**
	(0.027)
Difference	1.054**
	(0.240)

Finally, there are some concerns with using a time series model for this analysis that should be noted. The time series approach works best when the intervention point is clearly defined and when the expected change in outcome is observed in the near-term following the intervention (Bernal et. al, 2016). Since the expected effect of RDFs on new clinical trial starts in the disease is indirect, the expected time frame to observe a change in clinical trial activity is not immediate. It can take years for nonprofit organizations to ramp up operations, raise and deploy capital, and form strategic partnerships, and similarly, it can take years for researchers and firms to plan and fund clinical trials.

A.3: RDF Strategy & Clinical Activity, Additional Empirical Details

Table A.3.1: Explanation of Cases Where Event Year Differs from Year of RDF Establishment

Disease (RDF)	RDF year est.	Event year	Explanation
Angioma (Alliance)	2002	2005	Organization did not begin engaging in scientific research until 2005 with first conference hosted
Barth Syndrome (Foundation)	2001	2003	First research grants started in 2003
Cardio-facio-cutaneous syndrome (Cardiofaciocutaneous Int'l)	1999	2004	First research efforts started in 2004
Facioscapulohumeral muscular dystrophy (FSHD Society)	1992	2010	Initially founded as patient support organization. The genetic mechanism was discovered in 2010 for the disease, which is when the foundation transitioned to research-related activity
Friedreich's Ataxia (Research Alliance)	1998	2005	Initially founded as volunteer patient support group. In 2005, transitioned to staffed organization with research objectives
Phelan-Mcdermid Syndrome (Foundation)	2003	2011	First research related activities were patient registry and biorepository started in 2011 & 2012
Wilson / Hepatolenticular (Wilson Disease Association)	1985	2006	First research efforts and grant program were not started until 2006

Sources: Foundation websites; GuideStar Pro

Table A.3.2: Variables Used in Empirical Analysis

Variable name	description	source	mean	sd	range
Event_yr	year RDF was established or commenced research activity*	Form 990, RDF sites	2007.20	4.68	1997-2014
Active	Binary indicator for whether the disease is ever treated meaning the foundation is classified as active vs. passive	See "number_ activities"	0.58	0.49	0-1
PostRDF	Binary indicator for whether the observation year occurred pre or post the event year; 1 for every time period including and after the event year, 0 for every period before	n/a	0.50	0.50	0-1
Trialstarts	Number of new clinical trial starts in disease (i) at time (t)	Cortellis	1.13	2.93	0-33
AnnualRDFSpend	Yearly foundation spending in the disease, millions USD	Form 990	0.46	1.53	0.00-22.82
InitialRDFSpend	5 year annualized, millions USD	Form 990	0.55	1.22	0.00-7.85
PriorNIHSpend	5 year annualized, millions USD	NIH	1.87	3.50	0.00-19.63
Number activities *(not used directly in models)*	Number of research activities RDF pursues beyond traditional grantmaking; used to calculate "active"	RDF websites			

*in a few cases the RDF was established as a patient support organization rather than a research foundation. The event year corresponds to the year in which the foundation adopted its first research-related activity (e.g., funded first grant). See Appendix C, Table 1 for specific details.

Table A.3.3: Poisson Fixed Effects Model Output

Empirical models are also estimated using disease fixed effects. The sign and statistical significance for all coefficients remains the same as the primary estimations. Concerns with this approach include: dropping 8 diseases (7 from passive group, 1 from active group) where the dependent variable does not vary with time because no trials were started in the disease during the observation period, inability to control for relevant time invariant factors, such as NIH funding in the disease prior to RDF establishment, and dropping of one of the key indicator variables, active, because there is no within group variation.

	Model (dependent variable is annual new clinical trial starts)		
Poisson FE Estimations	(1) Avg Pre - Post Effect	(2) ...w/ 2 post periods	(3) ...w/ 2 pre & post periods
Active	omitted (does not vary within group)		
PostRDF	1.507**		
	(0.128)		
$PreRDF_{(years\ -5\ to\ -1)}$			1.012**
			(0.340)
$PostRDF_{(years\ 0-4)}$		1.204**	1.833**
		(0.170)	(0.294)
$PostRDF_{(years\ 5\ plus)}$		1.747**	2.376**
		(0.138)	(0.287)
ActiveXPostRDF	0.794**		
	(0.216)		
$ActiveXPreRDF_{(years\ -5\ to\ -1)}$			0.186
			(0.417)
$ActiveXPostRDF_{(years\ 0-4)}$		0.321	0.461
		(0.225)	(0.400)
$ActiveXPostRDF_{(years\ 5\ plus)}$		0.833**	0.973*
		(0.219)	(0.382)
Observations	1,313	1,313	1,313
Number of diseases	58	58	58
Num. with passive RDF	21	21	21
Num. with active RDF	37	37	37
Disease Fixed Effects	Yes	Yes	Yes

Robust standard errors in parentheses
** p<0.01, * p<0.05, + p<0.1

B: Appendix to Chapter 2

B.1 Identifying Orphan NMEs with RDF Support in Clinical Development

Table B.1.1 List of Orphan NMEs with Verified RDF Support in Clinical Development

Drug	Year	Indication	Foundation: Firm	Source
Besremi	2021	Polycythemia Vera	MPN Research Foundation: PharmaEssentia	Foundation site
Truseltiq	2021	Cholangiocarcinoma	Cholangiocarcinoma Foundation: QED Therapeutics	Firm website, RDF website
Oxlumo	2020	Hyperoxaluria Type 1	Oxalosis & Hyperoxaluria Foundation: Alnylam Pharmaceutical	Firm PRs, FDA, RDF
Zokinvy	2020	Progeria	Progeria Research Foundation: Eiger BioPharmaceuticals	Venture deals, Ct.gov, Firm site
Enspryng	2020	Neuromyelitis Optica	Guthy Jackson Foundation: Genentech	Firm PR
Viltepso	2020	Duchenne Dystrophy	Jett Foundation: NS Pharma	RDF site, ct.gov
Evrysdi	2020	Spinal Muscular Atrophy	SMA Foundation: Roche	Interviews w/ Roche, SMAF
Uplizna	2020	Neuromyelitis Optica	Guthy Jackson Charitable Foundation: Viela Bio	Firm PR
Qinlock	2020	Gastrointestinal stromal tumor	Life Raft Group: Deciphera Pharmaceuticals	Firm site, RDF site
Koselug	2020	Neurofibromatosis I	Children's Tumor: AstraZeneca	RDF site, article
Sarclisa	2020	Multiple Myeloma	Multiple Myeloma Research Foundation: Sanofi	RDF site; Venture deals
Ayvakit	2020	Gastrointestinal stromal tumor	Life Raft Group: Blueprint Medicines	FDA, RDF site
Vyondys 53	2019	Duchenne Dystrophy	CureDuchenne: Sarepta Therapeutics	Venture deals, RDF site
Trikafta	2019	Cystic Fibrosis	Cystic Fibrosis Foundation: Vertex	Venture deals, RDF site
Xpovio	2019	Multiple Myeloma	Multiple Myeloma Research Foundation: Karyopharm Therapeutic	RDF site; Venture deals
Tegsedi	2018	Transthyretin amyloidosis	Amyloidosis Research Consortium: Ionis	Firm site
Symdeko	2018	Cystic Fibrosis	Cystic Fibrosis Foundation: Vertex	Venture; RDF
Spinraza	2016	Spinal Muscular Atrophy	SMA Foundation: Biogen, Ionis	Interviews w/ Ionis
Exondys 51	2016	Duchenne Dystrophy	CureDuchenne; Charley's Fund: Sarepta	Venture deals
Empliciti	2015	Multiple Myeloma	Multiple Myeloma Research Consortium: Bristol-Myers Squibb	RDF site; Venture deals
Ninlaro	2015	Multiple Myeloma	Multiple Myeloma Research Consortium: Millennium Pharma	RDF site; Venture deals
Darzalex	2015	Multiple Myeloma	Multiple Myeloma Research Foundation: Janssen Biotech	RDF site; Venture deals
Orkambi	2015	Cystic Fibrosis	Cystic Fibrosis Foundation: Vertex	Venture deals
Farydak	2015	Multiple Myeloma	Multiple Myeloma Research Foundation: Novartis	RDF site; Venture deals
Keytruda	2014	Metastatic Melanoma	Melanoma Research Alliance: Merck	Ct.gov, 3rd party site
Pomalyst	2013	Multiple Myeloma	Multiple Myeloma Research Consortium: Celgene	RDF site; Venture deals
Kyprolis	2012	Multiple Myeloma	Multiple Myeloma Research Consortium: Onyx Pharmaceuticals	RDF site; Venture deals
Kalydeco	2012	Cystic Fibrosis	Cystic Fibrosis Foundation: Vertex	Venture deals

B.2: Robustness Checks

In robustness checks, novel (NME) orphan drugs excluded from Cohorts 1 & 2 in the main analysis are analyzed as "B" subgroups for each cohort. Subgroup "A" includes the drugs used in the main analysis. The statistically significant difference in average clinical development duration between Cohort 1 and Cohort 2 persists when considering subgroups.

Figure B.2.1 Cohort Study Design including A & B Subgroups

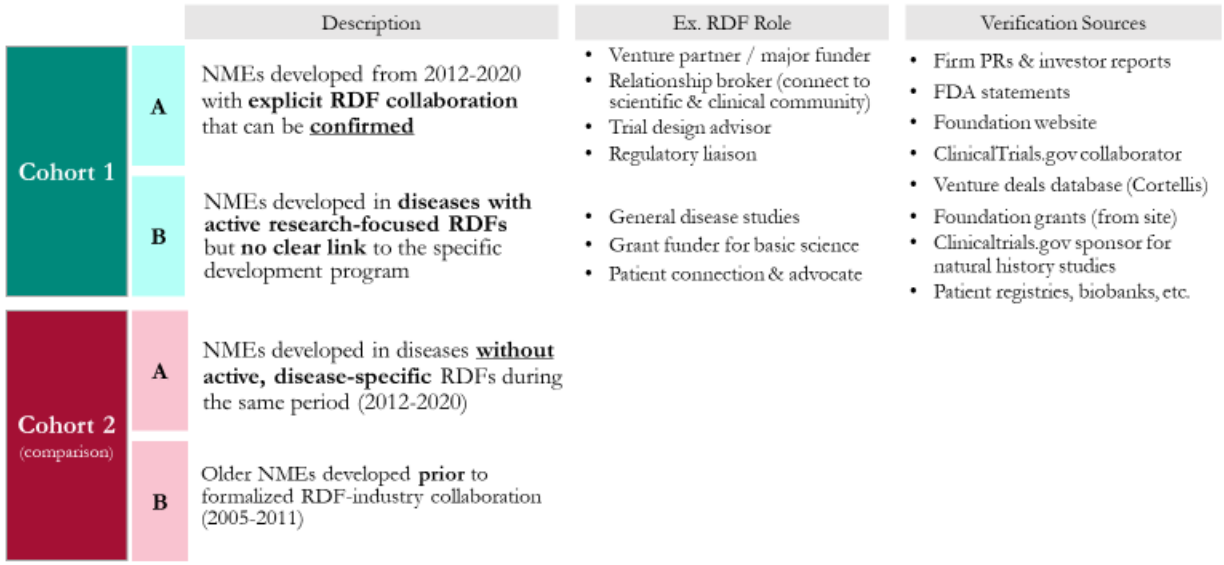
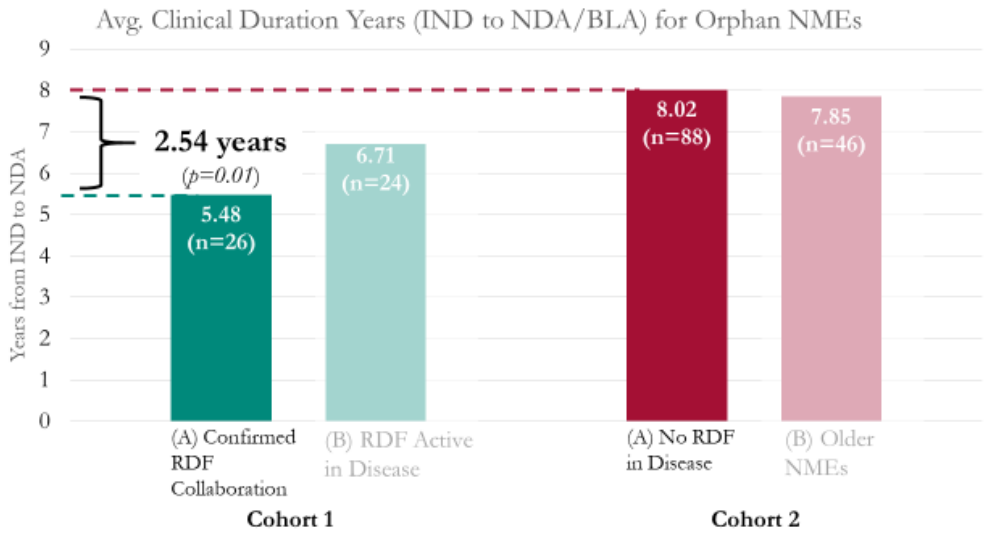


Figure B.2.2: Average Clinical Durations Including A & B Subgroups



B.3: Additional Descriptive Statistics

Table B.3.1: Disease-level Comparisons Across Cohorts

This table considers the unique diseases targeted by drugs in each cohort.

	Cohort 1	**Cohort 2 (Comparison)**
Description	**Diseases** targeted by orphan NMEs developed with confirmed RDF collaboration	**Diseases** targeted by orphan NMEs with no RDF active in the disease
Total unique diseases	13	57
Oncology	31% (4)	35% (20)
Monogenic	54% (7)	26% (15)
Prevalence Ultra-rare Rare Threshold	 31% (4) 62% (8) 8% (1)	 33% (19) 56% (32) 11% (6)

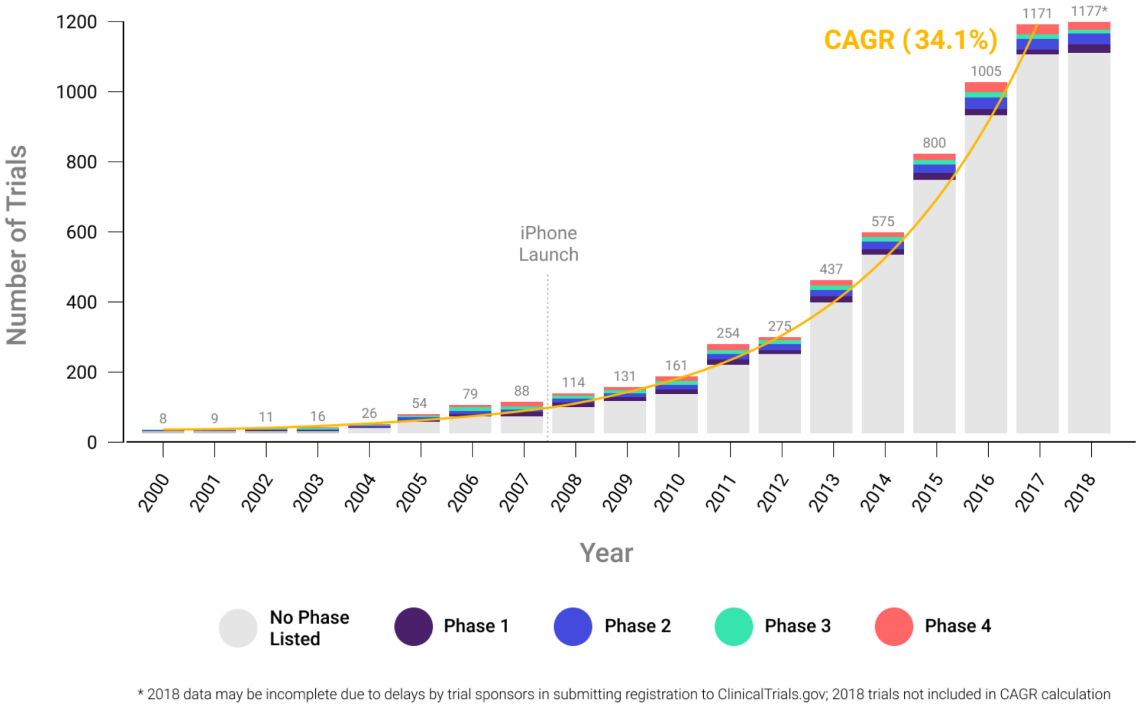
Note: Ultra-rare defined as fewer than 6,500 U.S. patients. Threshold defined as greater than 100,000 U.S. patients.

C: Appendix to Chapter 3

C.1: Additional Figures Depicting Use of DHTs in Clinical Trials

The below two figures were prepared for our prior work and appears in the npj Digital Medicine publication "Quantifying the use of connected digital products in clinical research" (Marra et al., 2020).

Figure C.1.1: Clinical trials using connected digital products by study start year and phase



Notes: 1) Each bar represents the total number of clinical trials started annually that include a connected digital product. The trials are segmented by phase, as designated in the ClinicalTrials.gov record. 2) "Connected digital products" is prior terminology used before the definition for "digital health technologies (DHT)" was established. The definitions are highly similar and the product types included in both are the same.

Source: Marra C, Chen JL, Coravos A, Stern AD. Quantifying the use of connected digital products in clinical research. *npj Digit Med.* 2020;3(1):50. doi:10.1038/s41746-020-0259-x

Figure C.1.2: Classifications of connected digital product use in clinical trials

Use Case	Description	Example
1  Trial **validates** digital product's **functionality**	Endpoints compare measurements taken by the product to measurements collected via other validated products/means	Trial validated that Spry Health's loop band is equivalent to standard methods (arterial line) in measuring vitals of COPD patients during surgery (NCT03240926)
2  Trial tests digital product's **clinical usability**	Endpoints relate to product's usability, which may include safety, tolerability, comfort, patient engagement or retention, patient adherence to a program, cost, comparative effectiveness, etc.	Trial tested usability of the Monica AN24, a continuous fetal heart rate device worn by the mother. Endpoints assess the mother's experience wearing the monitor and any change in her anxiety levels (NCT03370822)
3  Trial uses digital product to **capture endpoint data** for another intervention or **data of interest** in an observational study	Data captured by the product is used either explicitly or implicitly to inform an endpoint for another intervention (e.g., a drug, device, or behavioral intervention) or collects data relevant to the stated objective of an observational trial	Trial tested whether different types of aerobic exercise programs improve sleep quality. Researchers used the Actiwatch (a connected actigraph product) to capture movement data for one of the study endpoints (NCT03853668)
4  Trial uses digital product as the primary **intervention** or a **digital therapeutic**	Endpoints relate directly to product's effectiveness in bringing about change in the intended clinical or behavioral metric(s)	Trial testing whether digital cognitive behavioral therapy for insomnia (Sleepio) can increase sleep time and improve quality of life measures in patients with HIV vs. existing sleep hygiene recommendations (NCT02571595)

Notes

- Use cases 1, 3, 4 are mutually exclusive, meaning a single product cannot be used as described in cases 1&3, 1&4, or 3&4 in the same clinical trial. However, when more than one product is used in the same trial, these combinations are possible. For example, one product may be tested as the intervention (case 4) and another product may be used to measure a trial endpoint (case 3)
- However, a single product can be tested as in use cases 1,3,4 in combination with use case 2. For example, in a clinical trial that tests a product as an intervention, researchers may also include endpoints to assess the product's usability, such as patient satisfaction with treatment

Notes: 1. In this study, use cases 1 & 2 defined in the figure above (usability and validation) are combined into a single category termed "verification and validation". 2. "Connected digital products" is prior terminology used before the definition for "digital health technologies (DHT)" was established. The definitions are highly similar and the product types included in both are the same.

Source: Marra C, Chen JL, Coravos A, Stern AD. Quantifying the use of connected digital products in clinical research. *npj Digit Med.* 2020;3(1):50. doi:10.1038/s41746-020-0259-x

C.2: DHT Search Term List

The below list includes the full set of terms (n=1128) used in our text search algorithm to flag clinical trials that used a DHT. The terms are a mix of branded product names and general, unbranded product types. This list has been supplemented with additional terms from prior work in Marra et al. 2020 and Marra et al. 2021.

Newly included terms (n=110):

activity_monitor
aim_covid19_app
amazon_alexa
app_based_practice
awareness_bracelet
biosensor
biovitals
brave_program
cct_game
chat_based_support
collected_online
conducted_online
cont_glucose_monitor
covid19_symptom_tracker
digital_app
digital_cardiac_counseling
digital_counseling
digital_data_collection
digital_video_camera
e_learning

electronic_data_collection
electronic_patient_journal
electronic_questionnaire
exercise_bracelet
facebook
fall_risk_bracelet
google
handheld_manometer
handheld_spirometer
health_app
hear_glue_ear_app
home_pulse_oximeter
hwa_watch
hydration_sensor
i_neb
ICOPE_App
intelligent_pulse_oximeter
internet
meditation_app
mindfulness_app
miro
movehero
ncapp
newsfeed
noncontact_ecg
online class
online_coaching
online_contact
online_daily_diary
online_exercise
online_fall_detection
online_forum
online_group
online_intervention
online_learning
online_meeting
online_mindfulness
online_platform
online_questionnaire
online_selfadministered
online_selfcompleted
online_support
online_survey
online_trial
phone_app
post_online
qualtrics
redcap
reminder_bracelet
remote_assessment
remote_consultation
remote_mindfulness_session
remote_monitoring
secure_electronic_ecrf
skype
sleep_sense
smart_bracelet
smart_care_vip
smart_pill
smart_tv
social_media
tablet_based_games
teleconsultation
telehealth
telemedicine
telerehabilitation
text_message
thermal_sensor
vibrolung
video_based
video_call
video_communication
video_consultation
video_encounters
video_observation
videoconferencing
videophone_call
virtual check-in
virtual_care_at_home
virtual_clinic
virtual_group
virtual_reality
virtual_visit
web_application
webex
wechat
whatsapp
zoom
video_chat
online_yoga

Search Terms from Marra et al. 2020 (n=1018):

_10s_fork
_7000a_finger_probe_
accucheck
accu_check
accuchek
accu_chek
accugait
accupedo
achillex
actical
actigraph

actiheart

actisleep

actitrac

activepal

activepers

activity_monitor_comparison

activpal

actiware

actiwatch

actiwatch_spectrum

actiwatch_64

actofit

actofit_smartscale

adamm

adherium

adidas_zone

adis16400bmlz

adlcare

adxl_335

adxl105jqc

adxl330

adxl345

adxl346

agamatrix

aiocare

airbeam

aircurve

airsense

akern_bioresearch

akili

alcohoot_edge

alex_namu

alvita_optimized_pedometer

am1_

amazfit

ambiotex

ambygear

amiigo

android

apdm

apnea_risk_evaluation_system

apnealink

apnea_link

apostherapy

apple_health

apple_watch

aquagenie

aquapulse

armour39

ascensia_diabetes

asus_phone

athos_full_body

athos_leggings

athos_shirt

atlas_shape

atlas_wristband

auto_device_asthma_monitor

autoset_s8

autoset_s9

avant_2120

avant_tabletop

aw64

aw_64

awair_baby

awair_glow

aware_headphones

axivity

b_o_l_t

baby_gigl

baby_smartband

baby_vida

baby_wireless_thermometer

bagnoli

bahr_monitor

balansens

basis_peak

bayer_breeze

bayer_contour

beam_brush

beam_toothbrush

beddit

beddr

beets_blu

beetsblu

bellabeat

better_therapeutics

bg_star

bgstar

bi_sl2_breathalyzer

bi_sobrietor

bi_tad_monitor

bia_sports_watch

biancamed

bioharness

biomeme

biosensics

biosport_earbuds

biostamp

biostamprc

biostrap

biotelemetry

blipcare

blitz_smart_watch

blocks_modular_watch

bloomlife

blueair_aware

bluemaestro

bluesmart_mia

bluestar_app

bluetooth_blood_pressure

bluetooth_enabled_blood_pressure

bluetooth_posture_step_tracker

bluetooth_scale

bluetooth_thermometer

bluetooth_linked_thermometer

btooth_enabled_bathroom_scale

btooth_enabled_blood_pressure_

bluetooth_enabled_scale

bodimetrics

body_organ_life_tracker

bodybugg

bodyguardian

bodymedia

bodytrak

boil_and_bite_mouthguard

bp1_blood_pressure

bp2_blood_pressure_monitor

bpmphysio

bragi

breas_medical

breas_sweden

breas_vivo

breas_

breathemate

breathing_baby_monitor

breathometer

breeze_2_meter

breeze2

bresodx

bresotec

bruxoff

bsxinsight

bts_bioengineering

camntech

cardea_solo

cardiacdesigns

cardiacsense

cardiokey

cardiolight

cardiomedix

cardiosecur

cardioskin

care_predict_tempo

caretaker_medical

caretaker4

carrot_sense

centrepoint_insight_watch

cercacor

checkme

choicemmed

choicemmed_md100e

chrono_quit_smoking_solution

cicer

clearsky_t6

clevercap

clinicloud

cloud_dx

co_breath_sensor

coaguchek

cocoon_cam

code4armour

cogito

cognision

cognoa

cohero_health

contour_link

contour_next

contour_xt

cookoo_2

coros_watch

cosinuss

cpap_s9_series

cyberglove

dario_bgms

dario_blood_glucose

darma_pro

darma_sleep

deloitte_smart_helmet

delsys

dexcom

diabeo

digi_walker_

digital_accelerometer

digital_biomarker

digital_camera

digital_therapeutic

digitsole

dip_io

dorsavi_sensor

dreem

duofertility

dycare_rehub

dynaport

dynosense

e4_wristband

earlysense

eartrumpet

ecgmove

echo_smart_patch

eko_devices

ekso_bionics

eksogt

electricfoxy

elemnt

ember_sport

embletta

embletta_device

embrace_watch

emfit

emotion_faros

emotiv_epoc

emotiv_insight

empatica

emwave_2

enlite

epatch

epi_mobile_health

epoc_by_emotiv

epson_watch

equivital

e_series_psg

eshirt

esight

eva_colpo

eveline_fertility

everion

everon

eversense

eyenetra

eyeque

eyes_on_glasses

f_a_b__system

faros_360

faros_ecg

fever_scout

fingertip_pulse_oximeter

fitbit

fitbit_aria

fitbit_charge

fitbit_flex_2

fitglance

fitguard

fitmate

fitmeter

fitness_tracker

flyfit

fora_2_in_1

fora_system

fossil_smartwatch

fox_insight_app

fox_insight_self

fr74_hrm_earphone

free_style_freedom

free_style_insulinx

free_style_libre

free_style_lite

free_style_navigator

free_style_precision

freeemg

freescan

freespira

freestyle_freedom

freestyle_insulinx

freestyle_libre

freestyle_lite

freestyle_navigator

freestyle_precision

freewavz

fridababy

fuelband_se

functional_assess_biomech_system

g4_platinum

g5_platinum

gait_up

galaxy_s4

galaxy_s5

galaxy_s6

galaxy_s7

galaxy_s8

galaxy_sii

galaxy_tab

galvanic_pip

garmin

garmin_forerunner

geneactiv

geopalz

ginger_io

glucome

glucoscout

glucotel

glucotrack

glucowizzard

gluten_sensor

go2_achieve

gobe2

googlefit

gospiro

gow_heart

gt3x_

gt9x_link

guardian_connect

guardian_real_time

guardian_real_time_

guardian_sensor

g_walk

gyenno_spoon

h2opal

hailie_smart

hal_lower_limb_non medical

hal_lumbar_care_support

hal_lumbar_labor_support

hal_peripherals

hal_single_joint

handheld_pulse_oximeter

hapifork

happify

headspace_health

healthband

healthkit

healthpatch

heartcheck

heartguide

heartmath

heartrak

heartscan

heartscope

heddoko

helios_smart_ring

helo_classic

helo_lx

herotracker

hexoskin

hidrate

hijiband

holland_hybrid

holter_monitor

huawei_band

huawei_color

huawei_fit

huawei_talkband

huawei_watch

huinno

humon_hex

hxm_heart

hxm_smart

hydracoach

hyginex_sensor

hygreen_hand_hygiene

ibeat_wristwatch

ibgstar

ibrain

ichoice

ideea

idm_perform_footbeds

ifit_axis

ifit_vue

iglucose

ihealth

ihealth_wless_bpressure_monitor

iheart

imotions

inbody_band

inertial_measurement_units

inpen

insole_sensor

instabeat

insulet

insulia

inui_home_urine_analysis_test

iota_tracker

ipad

iphone

ipod

ipro_cgm

ipro_continuous

ipro_glucose

iproven_thermometer

ir20_ear_thermometer

iriveron

ironman_sleek

istride

ithermometer

ivyhealth_body_analysis_scale

jabra_elite

jabra_sport

jaeger_am2

jawbone_up

jazz_wireless

kaia

kanega

kardia_band

kardia_heart

kardia_mobile

kardia

kardiaband

kardiamobile

kehel

kenz

kid_power_band

kinect

kinesia

kingston_bracelet

kinsa_thermometer

kionix

kolibree_tooth_brush

koogeek_scale

koogeek_thermometer

leaf_nature

leaf_sensor

leaf_urban

leapband

lechal_smart

legsys

leikr_1_watch

level_smart_glasses

levl

lg_watch

lief_therapeutics

lifeband

lifebeam

lifecorder

lifefuels_bottle

lifelight

lifetrak

lifevest

logicink

loop_band

lowdown_focus

lully_sleep_guardian

lumafit

lumee

lumo_lift

lumo_run

luna_watch

lvl_hydration

mad_apparel

magik_toothbrush

mars_holter

masimo_radius

master_caution

mbody

med_reminder

medminder

med_reminder_

medrhythms

medsignals

medtronic_biomodule

medtronic_carelink

medtronic_minimed

mente_autism

metamax_3b

metamax3b

metria_sensor

mevics

mhealth

mi_band

micoach

micropem

microsoft_band

microsoft_band_2

milestone_sports_pod

milo_sens_blood_alcohol_track

minimed_paradigm

minimed_paradigm_real_time_revel

minimed_revel

minimitter

mini_mitter

miniwear_smart_watch

mio_fuse

mio_heart_rate_monitor

mio_slice

mio_watch

mio_wristband

mira_fertility

misfit

misfit_app

misfit_flash

mixfree_sports_watch

mma7260q_accelerometer

mma7361_accelerometer

mobile_app

mobile_device

mobile_ecg

mobile_eeg

monbaby

monica_an24

monterey_hybrid

moov_hr

moov_now

moticonscience

motionlogger

motionwatch

motiv_ring

moto_360

motoactv

motorola_droid

motorola_smart_phone

movemonitor

movesense

movisens

mpu6050

mshorts

mspirometer

mtw_awinda

multisense

muse_headband

muse_meditation

my_uv_patch

mybabyscale

mycite

mycoach_pulse

mygluco

myoxy

myspiroo

mystar

mystar_dosecoach

mystar_extra

mytens

mythermo

myzone

nabi_compete

nabu_x

nadi_x

namu_alex

nanit

nanit_insights

neofect

neptune_pine

neuroon_open

neurosky

neurotracker

nevo_watch

nexus6

nightware

nike_fuelband

nike_sensor

nike_sportswatch

nintendo_wii

nokia_blood_pressure_monitor

nokia_body

nokia_bpm

nokia_go

nokia_steel

nokia_thermo

nonin_3230_pulse_oximeter

nonin_onyx_ii

nonin_pulse_oximet

nonin_pulse_oximeter

noraxon_software

northeast_monitoring

nosefrida

notch_motion_capture

noteband

nox_music

nox_sleep_light

nox_t3_

nox_t3

nuerotrail

olfinity

olympus_ls5

omada_health

omate

omnipod

omron

onduo_app

one_drop_premium

onetouch

onyx_vantage

opal_device

opernative

optalert

optimeye

oral_b_7000

orcam

orpyx

oura_ring

oxitone

oxitone_1000

oxxiom

oxywatch

ozmo_active

pacifier_thermometer

pal_technologies

palmsat

palo_alto_health_sciences

pam_am101

pam_am300

pamsys

pavlok

pavlok_2

pear_therapeutics

pebble_activity_monitor

pebble_monitor

pebble_watch

peerbridge

personal_vision_tracker

philips_actiwatch

philips_body_analysis_scale

philips_dti_2

philips_ear_thermometer

philips_gosafe

philips_health_watch

philips_lifeline

philips_upper_arm_blood_pressure

philips_wrist_blood_pressure

physilog

physiotrace

physiowave

pivot_breath_sensor

pivotal_living_band

pixie_smart_pads

pkmas

plume_labs_flow

polar_a300

polar_a360

polar_a370

polar_active_watch

polar_axn500

polar_axn700

polar_balance

polar_beat

polar_coach

polar_cs

polar_electro

polar_f11

polar_f55

polar_f6

polar_f7

polar_flow_for_club

polar_ft

polar_h10

polar_heart_rate_sensor

polar_loop

polar_m200

polar_m400

polar_m430

polar_m450

polar_m600

polar_oh1

polar_rc

polar_rs

polar_s410

polar_s510

polar_s520

polar_s610

polar_s625x

polar_s710

polar_s720i

polar_s725

polar_s810i

polar_sleep_plus

polar_t31

polar_teampro

polar_v650

polar_v800

polar_vantage

popit

portable_albumin_tester

pour_moi

prana_tech

pressure_guardian

pressureguardian

pressuretel

professional_care_7000

propeller_health

prosense_watch

proteus_digital_health

proteus_discover

protokinetics_zeno

pryme_vessyl

pulsox_300

pulsox_300_

push_band

qardio_arm

qardioarm

qardiobase

qardiocore

q_poc

qsun

quardio_base

quardio_core

quatix

quell_device

quick_care_thermometer

quicksee

radar_pace

rapael

rapael_smart

rayvs1

readiband

recon_jet

reemo

rehacom

relion

remedy_digital_scale

remote_monitoring_device

rempark_system

renault_sport_t_shirt

researchkit

resmed_s9

resperate

reston_z

rhealthx1

ringly_luxe

ringly_smart

rootirx

rpm_bp

rpm_scale

rpm_bp100

rpm_scale100

runscribe

runsense_watch

ruputer

s3_connected_health

s8_escape

s9_autoset

s9_vpap

s9_resmed

safebeing

samsung_galaxy

samsung_gear

scallop_touchscreen

scanadu_scout

screeneye_x

seeq

sense_with_voice_sleep

senseonics

sense_u

sensewear

sensor_dot

sensor_insole

sensoria_heart_rate_monitor

sensoria_socks

sensoria_sports_bra

sensoria_tshirt

sensoria_t_shirt

sensoscan

sensyu

sentio_feel_wristband

shade_ultraviolet_sensor

shapa

shft_run

shimmer_sensor

shimmer3

silver_mother

silvercloud

simpill

sippo

siren_diabetic_socks

sleep_dot

sleep_monitor

sleep_profiler

sleep_shepherd

sleep_tracker

sleepio

sleepminder

sleeppeanut

sleeptracker

smart_apparel

smart_bed_sheet

smart_body_analyzer

smart_bra

smart_brush

smart_doppler_fetal_monitor

smart_ear_thermometer

smart_garment

smart_glasses

smart_glove

smart_glucose_meter

smart_headphone

smart_inhaler

smart_insole

smart_kid_scale

smart_phone

smart_pill_bottle

smart_powered_toothbrush

smart_scale

smart_shoe_insole

smart_sock

smart_stick_thermometer

smart_technology

smart_textile

smart_thermometer

smart_toothbrush

smart_watch

smart_workout_gloves

smartband

smartbra

smartcap

smartex

smartinhaler

smartphone

smartphone_breathalyzer

smartscale

smartshoe

smartsleep

smarttemp

smartturbo

smartwatch

smokebeat

snap40

solos_cycling_glasses

somaxis_cricket

somnowatch

sonomat

sony_playstation

sony_smart_b

sony_smartband

sony_smartwatch

sound_level_meter_app

soundsport_wireless

spark_watch

spire_health_tag

spire_stone

spirodoc

spirotel

spotnsave_band

spree_headband

spree_smartcap

sproutling_baby_monitor

sproutling_smart_sleep

spry_health_loop

spry_loop

sqord

stealth_system_ecg_recorder

stepwatch

stethee

strava

stridalyzer

striiv_apex

sugarbeat

sunbit

sunsprite

surrosense_rx

suunto

suunto_spartan

sync_burn

sync_calorie

sync_distance

sync_elite

sync_fit

sync_gps

sync_step

sync_watch

synertial_igs_180

t__slim

tabletop_pulse_oximeter

tactix

tandem_diabetes_care

tandem_insulin_pump

tb_breathalyser

telcare_2_0_bgm

telcare_blood_glucose_meter

telcare_glucometer

temptraq

texas_instruments_wearit

the_pip

the_quell

thermos_bottle

ti_wearit

tickr

tinke

tiny_logics_memo

tlink_watch

tm_750_thermometer

tmjoint

tobii

tobii_pro

tom_tom_spark

tomtom

tomtom_runner

tomtom_spark

tosense_cova

touch_tracker

touchhb

trago_bottle

triggerfish

trigno

true_metrix

truemetrix

trueresult

truetrack

tslim

t_slim

tyto

tzoa_haven

ua_band

ua_heart_rate

ua_hovr

ua_651ble_blood_pressure

uc_352ble_scale

uchek

ulla_hydration_reminder

umana_t1

under_armour

under_armour_band

under_armour_burn

under_armour_calorie

under_armour_distance

under_armour_elite

under_armour_fit

under_armour_fitness_tracker

under_armour_heart_rate

under_armour_hovr

under_armour_sync

upright_go

upright_pro

valedo

varia_vision

variable_node_co2

vector_mouthguard

verily_study_watch

versame_starling

vibe_5atm

vibe_hiking

vigo_fatigue_monitor

viiiiva_heart_rate_monitor

vimove

vincense

visi_mobile

vital_moto_mod

vital_scout

vitality_glowcap

vitalograph

vitalpatch

vitalsense

vitalsignals

vitascan

vivoactive

vivofit

vivoki

vivomove

vivosense

vivosmart

vívosmart

vivosport

vivowatch

voluntis

vue_smart_glasses

wme_wristband

wahoo_fitness

walking_style_pro

walking_style_x

watchpat

wavelet_clip

wavelet_sensor

wavelet_wristband

wearable

wearable_defibrillator

wearable_gym

wearable_uv_sensor

weighttel

wellograph_watch

wherecom_k3

wing_device

wireless_arm_bpressure_monitor

wireless_weight_scale

wireless_wrist_bpressure_monitor

withings

witscale

wiwe

wordle

wristox

wynd_air_quality_tracker

wynd_essential

wynd_plus

x2_biosystems

xbox

x_doria

xiaomi

xmetrics

xpod_3012

xsens

yofimeter

ze_tel

zeband

zeblaze

zecircle

zeclock

zeeq

zefit

zen_sensor

zen_watch

zensor

zephone

zephyr_biopatch

zeraph

zeround

zesplash

zesport

zetime

zewatch

zikto

zio_patch

zio_xt_patch

zio_xt

zwift_runpod