Best Practices for Venture Philanthropy Collaborations between Disease-Focused Foundations and For-Profit Life Science Companies

by

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Abstract

The history of private philanthropy in the US has been dominated by family foundations with arms-length philanthropy practices that largely existed in separation from commercial enterprise and business operations. This paper looks at emerging organizational and funding models being used in a wide range of disease areas in which philanthropy has shifted towards a more "venture-oriented" model sometimes referred to as disease foundation venture philanthropy (DFVP) as practiced by disease focused foundations (DFFs). More specifically, this research seeks to understand how these models map onto the range of translational challenges confronted by those engaged in bringing ideas from the bench to the bedside and it explores our current understanding of DFVP best practices. It concludes by raising questions and addressing issues designed to assist those who seek to setup successful collaborations between DFFs and industry partners.

Background

Traditional Disease-Focused Philanthropy

The US has a long history of non-profit foundations active in biomedical research. Family foundations have long dominated the philanthropy industry, and their outsized influence exists to this day in well-known institutions such as the Carnegie Institution, Rockefeller Foundation, Howard Hughes Foundation and more recently, the Bill and Melinda Gates Foundation of $25B endowment fame. Historically, these foundations have had little or no general public input, controlled decision-making within a private context, and devoted themselves to arms-length grants funding activities in a somewhat noblesse oblige manner. Philanthropy was treated as and thought to be separate and distinct from commercial activities and business.

The Carnegie Institution for Science was one of the first major philanthropy players who focused on funding disease research. Founded in 1902 in Washington DC with $10M from the famed industrialist, Andrew Carnegie, the Carnegie Institution was intended to be an "independent research institution" devoted to expanding basic scientific knowledge. Grants were initially given to mostly non-medical studies (e.g. anthropology, economics, mathematics, etc). Over its 100 year history, the Carnegie Institution has expanded its research areas to medical-related studies the most well-known grants focusing on developmental biology and embryology. From its inception, the Carnegie Institution has sought to support "exceptional individuals" in their quest to solve "intriguing scientific questions." Carnegie scientists and researchers include luminaries
such as Alfred Hershey, who won the Nobel Prize in 1969 for his insights into virus replication and genetic structure, and Andrew Fire, who won the Nobel Prize in 2006 for discovery of RNA interference. 45

The Rockefeller Foundation has similarly had a broad range of interests with its mission to “promote the well-being of humanity.” Founded in 1913 by the New York State Legislature and endowed with the initial gift of $35M from John D. Rockefeller Sr., the Rockefeller Foundation has distributed over $14B in current dollars from its inception onward. In sharp contrast to the more hands on approach of philanthropist such as Bill Gates, John D. Rockefeller Sr. never attended any of the board meetings, claiming he had no knowledge of how best to carry out the mission of his eponymous philanthropy. Nevertheless, global and public health became an early priority for the Rockefeller Foundation with its focus on hookworm eradication, malaria, yellow fever, and schistosomiasis. Grants to medical and public health schools around the world also supported the education prong of its mission. Illustrious accomplishments, especially in the public health sector, span the entire history of the Rockefeller Foundation, starting with the development of the yellow fever vaccine for clinical use by the Max Theiler in the Foundation’s Virus Laboratory the 1930’s. (He eventually went on to receive the Nobel Prize in 1950.) The Foundation supported the development of the electron microscope in the 1940’s, the field of genetics in the 1950’s, an “international network” of scientists devoted to the “great neglected diseases” of the developing world known as the Great Neglected Disease Program in the 1970’s, a tropical disease research program in cooperation with the WHO in the 1980’s, and the Children’s Vaccine Initiative and the International AIDS Vaccine Initiative in the 1990’s. 46

The Albert and Mary Lasker Foundation was created in 1942 from fortunes from the advertising world to “support biomedical research” to conquer disease, improve human health, and extend life. Mary Lasker was a prominent and influential biomedical activist and helped to pass a bill to create the now National Health, Lung, and Blood Institute in 1948. The Lasker Foundation also lobbied for the passage of the National Cancer Act in 1971. According to the Lasker Foundation website, the Lasker Award is given annually to a researcher, scientist, or clinician who has made significant contributions towards the “understanding, diagnosis, treatment, cure, or prevention of human disease.” Seventy-six Lasker Award recipients have gone on to receive Nobel Prizes, so a Lasker prize augurs well for the awardees. Discoveries that have been awarded include the discovery of anti-TNF therapy for autoimmune diseases by Marc Feldmann and Ravinder N.
Maini, discovery of nuclear hormone receptors by Pierre Chambon, Ronald M. Evans, Elwood V. Jensen, the discovery of telomerase by Elizabeth Blackburn, Carol Greider, Jack Szotsak, and more. The Lasker Foundation is not a grant-making foundation, instead, it primarily uses prizes and awards as the means to highlight clinical science, basic science, and public service accomplishments.47

The John D. and Catherine T. MacArthur Foundation was created in 1975 by John MacArthur, one of the three wealthiest Americans at the time of his death. It is one of the 20 largest private philanthropic organizations in the US with a $1.8B endowment in 2008, and has awarded more than $4B over its lifetime. Its four main programs focus on global security and sustainability including human rights, human and community development, general program including public interest media, and the most famous, the MacArthur Fellows Program. The MacArthur Fellows Program, also known as the MacArthur “genius” award, grants 5-year unrestricted fellowships to 20-40 “individuals...who show exceptional merit and promise of continued creative work” per year.48

The March of Dimes Foundation was founded in 1938 as the National Foundation for Infantile Paralysis devoted to “decreasing [baby] birth defects, premature deaths, and infant mortality”. Originally conceived to fight polio, the March of Dimes Foundation supports research, community services, education, and advocacy, according to its website. The Foundation was founded by President Franklin D. Roosevelt, himself a polio victim, and was instrumental in funding Dr. Virginia Apgar, who developed the now universal Apgar system for evaluating newborn babies and legitimized a fledging specialty focused on newborns. In addition, the March of Dimes funded Dr. Jonas Salk’s and Dr. Albert Abin’s research into polio vaccines, and ran successful pilot tests with 1.83M US schoolchildren amidst significant public debate. After it achieved its mission of developing a polio vaccine, the March of Dimes Foundation shifted its efforts towards preventing premature deaths, defects, and decreasing infant mortality.49

**Professionalization of Philanthropists & Patients**

In the past few decades, the convergence of two trends has given rise to “venture philanthropy” in the biomedical space as a popular philanthropic operations philosophy. These two trends are the professionalization of the philanthropy industry, and the rising levels of patient education
and engagement. The commercialization of philanthropic practices has been reflected in more business-savvy backgrounds of recent foundation staff hires and adoption of performance metrics scorecards to measure success.

A perusal of the backgrounds of program directors 50, even 20 years ago would found few MBAs. The training of program directors of today’s philanthropies are, by and large, rooted in both academia and industry. In addition, venture philanthropy conferences such as those run by FasterCures bring together disease focused foundations in a systematic way to run seminars, present case studies, and network amongst themselves. Graduate degree programs like the Master of Arts in Philanthropic Studies at Indiana University’s Center on Philanthropy offer specific coursework in philanthropy. The Association of Fundraising Professionals and the Association of Healthcare Philanthropy offers seminars and certificate courses in venture philanthropy for its members. Cultural sociologists like Michael Moody at the University of Southern California have studied the construction and evolution of the venture philanthropy culture, further institutionalizing the venture philanthropy field.

Another sign of the maturation of the venture philanthropy industry is the rise of the venture philanthropy ecosystem. New advisory organizations, consulting groups (e.g. Center for Effective Philanthropy, Brigdespan), research firms (e.g. New Philanthropy Capital), and even philanthropic investment banks (e.g. Sea Chang Capital) have been coming into existence. FasterCures, a think tank devoted to transformative medical research enterprise, has even called for “medical research investment analysts” who would provide the same rigor of analysis into DFFs and their partners as Wall Street analysts.

Watch-dog organizations like Charity Navigator publish free annual quantitative scorecards of the 5,000 largest US-based charities. It utilizes publically-available tax returns to evaluate organizational efficiency and capacity. Charity Navigator breaks down expenses in program, administrative, and fundraising expenses in both percentages and absolute figures, and lists compensation figures for top leadership of the organization. American Institute of Philanthropy (AIP) is a similar organization that publishes the “Charity Rating Guide & Watchdog Report” with financial ratings on over 500 US charities.
On the clinical front, patient advocacy groups armed with online forums (such as those found on Patientslikeme.com) and access to unprecedented clinical and scientific information have pointedly criticized the lack of real results in the form of disease-modifying therapies commercialized from foundation-funded research. Many disease foundations that subscribe to venture philanthropy were founded by patients and affected families who were “frustrated by the slow pace of the traditional medical system.”4

The intense activism of the AIDS community, and its unprecedented engagement of basic scientists and researchers to develop diagnostics and treatments, paved the way for today’s high-touch patient advocacy approach. When AIDS and HIV was first discovered in 1980 and 1983 respectively, the AIDS activist community mobilized in high-prevalence cities (e.g. San Francisco, Paris) to engage local public health officials and federal regulators. These activists were sophisticated, highly-educated, media savvy individuals who used a variety of public awareness techniques (e.g. demonstrations, marches, sit-ins, lawsuits) to demand money, resources, and information. They strategically aligned themselves with scientists to educate themselves about the fledging AIDS science and push for better diagnostic and treatment options.4

Because of these scientifically-informed public advocacy activities, the FDA and NIH amended their policies to expand access to drugs in development, include AIDS and HIV-infected patients on protocol, research, and peer review committees and data safety monitoring boards. Crucially, the FDA was persuaded to adopt surrogate markers for HIV drugs that decreased development time for pharmaceutical companies, making it financially attractive for companies to increase R&D spend in this area. As a result, the New England Journal of Medicine reported that AIDS-related deaths had decreased by 67% in the US by 1998.14

**Venture Philanthropy**

Venture philanthropy is broadly described as applying for-profit business practices to non-profit operations.11,17 A key assumption that undergirds much of venture philanthropy is that fulfilling the philanthropic mission and creating value for “investors” (venture philanthropy-speak for donors and patients) are not mutually exclusive concepts.5 One of the earliest explications of
venture philanthropy is found in a seminal April 1997 Harvard Business Review article “Virtuous Capital: What Foundations Can Learn from Venture Capitalists”. In this article, Christine W. Letts, William Ryan, and Allen Grossman delineate the most relevant venture capitalist practices as applied to foundation funding models. They tackle six areas in particular: risk management, performance measures, closeness of the relationship, amount of funding, length of the relationship, and finally, the exit. Peter Frumkin in 2003 penned “Inside Venture Philanthropy”, one of the first broad look at the origin of venture philanthropy and the push by entrepreneurs to adopt business practices to solve problems in “traditional philanthropy.” In the press, the first usage of “venture philanthropy” was in the 1972 New York Times article about the Rockefeller Family Foundation. A search for the term “venture philanthropy” in the global press and other publications finds the number of hits increasing from 4 in 1998 to 105 in 2002 to 294 in 2009 for a CAGR of 8% from 2004 to 2009.

Much has been written about venture philanthropy in the past 10-20 years, including common characteristics found in most venture philanthropy models. Often described as “collaborative, mission-drive, strategic in their allocation of resources, and results-oriented”, this new breed of philanthropy was pioneered by entrepreneurs and newly-minted philanthropists. New wealth holders pointed to the seeming lack of effectiveness and impact of organized philanthropy. Meaningful advances in many of the areas that organizations targeted such as public health, health care, and public education seemed sparse and scattered. The rise of venture philanthropy shadowed the dot-com boom in the 1990's with good reason; the founders of successful ventures relied heavily on venture capital practices to grow and be competitive. To this new breed of philanthropists, current grant-making processes seemed slow, unfocused, and lacking in clear performance measurement tools. The application of their successful business strategies to non-commercial interests seemed logical, and the fantastic wealth creation during this period helped drive early proponents of venture philanthropy especially in the software industry, most notably, Bill Gates.

There are as many working models and organizational forms as there are foundations, but key characteristics include:

- Faster grant-making
o Increasing the flexibility of grant-making by reducing bureaucratic red-tape with shorter grant applications, quicker review cycles, and granting funds on ongoing basis.

o Increasing agility of the DFF to respond more quickly to rapidly changing science discoveries with scientifically-informed program management.

• Shoring up financial sustainability of grantee by supporting long-term capital needs. Instead of thinking of grants in 1 year chunks, DFFs began to strategically allocate follow-on funds for potentially multi-year, successful programs.

  o Broadening and diversifying source of funds from one category (e.g. donations) to many (e.g. syndicate of investors).

  o Assisting with capital raising by connecting partners with high-net worth individuals from its donor pool and venture capitalists on the foundation’s Board of Directors, and even accompanying startups on the road to actively fundraise.

  o Engaging in a long-term relationship with the partner and being kept up-to-date on changing program and financial needs.

  o Signaling a “Good Housekeeping” seal of approval to the science behind the drug program to prospective partners and investors by independently vetting the company’s science.

• Funding “high risk, high reward” projects as a complement to NIH funding.

  o Defraying early financial risk by funding creative ideas with sound scientific basis.

  o Seeking “risky, innovative ideas that are likely to draw further funding down the road.”

  o Creating a market in the translational research space.

  o Supporting politically risky projects (e.g. stem cell research).

  o Proactively identifying & filling key gaps in public funding.

• Greater disclosure and accountability with transparent performance metrics.

  o Measuring impact-to-effectiveness ratios, negotiating and agreeing on time-dependent milestones between the grantor and grantee.

  o Unbiased 3rd party evaluation of grants.

• Closely connecting the donor “activist” and beneficiary with an interactive approach.
• Ranges from day-to-day operations involvement to high-level board seat
• High levels of engagement, increasing information flow and decreasing information asymmetry, including sharing of business expertise

• Applying good governance and management practices, developing organizational capabilities
  • Strategy, personnel and management support, training
  • Organizational capacity, infrastructure, and funding needs
• Acting as a hands-on facilitator, catalyst than a passive actor
  • Shifting from “oversight” mentality to “partner” relationship

**Current Landscape of Venture Philanthropists**

Venture philanthropy is a very malleable term. Like social enterprise, venture philanthropy has been defined so broadly in publications and the lay press that that its umbrella covers everything from microfinance to charter schools. As a catchphrase, venture philanthropy encompasses a universe of approaches. It simultaneously describes a protagonist and a process as well as very different relationships between various stakeholders. In most cases, the relationship resembles partnerships between venture capitalists and their respective portfolio companies. Listed below are few of many permutations:

• One Philanthropist Model
  • One wealthy funder-entrepreneur – One or multiple non-profit (e.g. Skoll Foundation’s Urgent Threats Fund, Gates Foundation, Andy Grove)
• Multiple Philanthropists Model
  • Syndicate of wealthy funder-entrepreneurs – One or multiple non-profit(s) (e.g. Silicon Valley Social Venture Fund)
  • Donations/services from many wealthy entrepreneurs – New “venture fund”/consulting foundation – One or multiple non-profits (e.g. Social Venture Partners)
• Secondary venture philanthropy funds Model
  • Venture capital fund – Off-shoot fund – One or multiple non-profits (e.g. Flatiron Future Fund)
- Established non-profit – Off-shoot fund – One or multiple investigators, one or multiple entities (both non-profit and for-profit) (e.g. James Irvine Foundation)

- Primary venture philanthropy funds Model
  - Established non-profit – For-profit entities (e.g. Cystic Fibrosis Foundation)
  - Foundation – Charities (Roberts Enterprise Development Fund)
  - Foundation – Foundation (Case Foundation – ABC)

As the examples above show, there are multiple relationship modalities. Additionally, the flow of money from the original donor to the final grantee can range from 1 (the donor gives money to the grantee organization or individual) to 3 (the donor gives money to a foundation, the foundation allocates grants to a charity, the charity uses these funds to support a grantee organization/individual). Nevertheless, all of these donors and organizations self-categorize themselves as practitioners of the venture philanthropy philosophy. As the field of venture philanthropy matures and is codified, the diversity of organizational models and practices continues to grow.

In a 2004 survey conducted by Rebecca Wyhof at the University of North Carolina at Chapel Hill, the nature of the nonprofit-venture philanthropy foundation relationship was characterized as being “involved, passionate, supportive, financially invested, proactive, engaged, accessible, and more committed than other funders.” 28 foundations were selected on a literature review, and included many noted organizations such as the Robin Hood Foundation, Social Venture Partners, The Broad Foundation, the Silicon Valley Social Venture Fund, etc. Three to four grantees per foundation were selected at random to receive a survey questionnaire to examine the administrative impact of “high-involvement” practices utilized by venture philanthropy funders. Survey respondents indicated that the financial commitment was only one of many resources that the foundation brought to bear on its grantees. The survey also noted that negative impressions to venture philanthropy included:

- Intrusive and controlling foundations
- Inexperienced investors who blindly applied for-profit business practices, where staff time was spent educating the funders
- Resentment amongst foundation staff: micromanaging and high-maintenance funders
Contrast with the NIH

Venture philanthropy papers typically raise the question of whether philanthropic donations guarantee better science than government or industry.\textsuperscript{26} I argue here that this is the wrong question. DFFs, NIH, and industry are all trying to solve, with some overlap, different problems within different business models and incentive structures. Each answers to a different set of constituencies. The NIH, for example, is accountable to the American public taxpayer via politicians. Thus its funding strictures reflect its conservative nature.\textsuperscript{3} The NIH and its member institutes select mostly low-risk, “safe” projects\textsuperscript{8,11}. The investigators who receive NIH funding have trended towards older age and greater seniority. Industry is answerable to its shareholders or private equity investors and is relentlessly focused on maximizing financial return. DFFs are accountable to its donors and patients, and focuses on filling translational gaps where NIH cannot go and industry finds insufficiently profitable. Although NIH funding dwarfs private funds for research in relative terms (e.g. $2.54B in NIH funding for Alzheimer’s research vs. $260M foundation monies from 1998 to 2007, not including Alzheimer Drug Discovery Foundation funding\textsuperscript{25}), DFFs have the freedom to funds riskier science with high potential clinical impact.

The NIH is not inured from public inquires to produce tangible results. Responding to criticisms that its research efforts were not assisting innovative therapies to move from bench to bedside, it created the NIH Roadmap for Medical Research to “catalyze” translational research. As NIH funding flows to specific areas, DFFs often react by supplementing and/or complementing in an attempt to maximize both government and private dollars. As the recent economic downturn shrinks endowments and drives down donations\textsuperscript{20,24}, private funds are stretched to complement NIH grants. The American Recovery Reinvestment Act (aka “stimulus bill”) injected an additional $10.5B into research funding, but most will still be allocated to basic research.\textsuperscript{7}

Prior to DFVP, DFFs hewed closely to the traditional NIH grant process. Most grants were given to researchers and investigators in university labs and academic medical centers (AMCs). However, in response to pressures to be more results oriented, venture philanthropic foundations have articulated their value drivers as producing multiplicative effects on their initial investments.\textsuperscript{2,16} The terminology shift from “grants” to “investments” signaled a change in how venture philanthropic foundations envisioned the relationship with their recipients. A grant implied a one-time, one-way transfer of funds with little or no follow-up or oversight. Additionally, grants have been and continue to be strongly associated with the NIH model of
basic science funding with its laissez faire feedback process. By rebranding grants as investments, the DFF value proposition has expanded to include non-financial resources. Often, this was and is called “innovation capital” or “risk capital” in venture philanthropy literature. (For the purposes of this paper, “grant” and “investment” will be used interchangeably). Additionally, “grantees” are often renamed as “partners”, subtly upending the power dynamic embedded in a grantor-grantee relationship.

Key value drivers that these venture philanthropic advocates assume that they will bring to a partnership include:

- Money
- Introductions to knowledgeable and wealthy people
- Neutral “safe” collaborative space
- Sophisticated media
- Access to technology

Venture philanthropy has been in vogue in areas such as education and global health (e.g. Medicines for Malaria Venture – 1999 global alliance partnered w/ industry to conduct clinical trials). Biomedical venture philanthropy has been led by global health, primarily championed by the Bill & Melinda Gates Foundation with its $25B endowment.

On a macro level, private non-for-profit support of biomedical research was estimated to have increased by 36% from $1.8B in 1994 to $2.5B in 2003 (inflation-adjusted numbers in 2003 dollars). Hamilton Moses’s source by source breakdown in this 2005 JAMA article, “Financial Anatomy of Biomedical Research”, show a stunning increase in biomedical research funds by pharmaceutical firms as reported by PhRMA, the umbrella organization for pharmaceutical companies. Sources included foundations, medical research organizations, free-standing research institutes, so the $2.5B in 2003 overstates the contribution of biomedical foundation. All US biomedical research funding was estimated to have doubled from $47.8B in 1994 to $94.3B in 2003 (inflation-adjusted numbers in 2003 dollars). The average breakdown by source was 57% industry, 28% NIH ($29B), 3-5% state-local government and private funds as seen in Table 1 below.
Table 1: Breakdown of Biomedical Research Funding by Source in US Billions (1994-2004)\(^9\)

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<td>$10.4</td>
<td>$10.9</td>
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<td>$6.9</td>
<td>$6.4</td>
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<td>State and local governments</td>
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<td>$2.8</td>
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<tr>
<td>Foundations, charities, and other private funds</td>
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<td>$1.6</td>
<td>$1.6</td>
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<td>$2.6</td>
<td>$2.6</td>
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<td>Pharmaceutical firms</td>
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<td>$11.9</td>
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<td>$15.5</td>
<td>$17.1</td>
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<td>$25.7</td>
<td>$27.0</td>
<td>$30.6</td>
</tr>
<tr>
<td>Biotechnology firms</td>
<td>$7.0</td>
<td>$7.7</td>
<td>$7.9</td>
<td>$9.0</td>
<td>$10.6</td>
<td>$10.7</td>
<td>$14.2</td>
<td>$15.7</td>
<td>$20.5</td>
<td>$17.9</td>
<td>$19.8</td>
</tr>
<tr>
<td>Medical device firms</td>
<td>$2.7</td>
<td>$3.4</td>
<td>$3.8</td>
<td>$4.4</td>
<td>$4.7</td>
<td>$5.3</td>
<td>$6.3</td>
<td>$7.3</td>
<td>$8.25</td>
<td>$9.2</td>
<td>$10.8</td>
</tr>
<tr>
<td>TOTAL</td>
<td>$37.1</td>
<td>$40.1</td>
<td>$43.1</td>
<td>$47.6</td>
<td>$52.9</td>
<td>$58.2</td>
<td>$71.0</td>
<td>$79.4</td>
<td>$90.9</td>
<td>$94.3</td>
<td>$94.5</td>
</tr>
</tbody>
</table>

ADJUSTED TOTAL*                      | $47.8  | $50.3  | $53.1  | $57.6  | $62.6  | $66.9  | $78.9  | $85.1  | $94.6  | $94.3  | N/A    |

*Adjusted Total = Adjusted by Biomedical Research and Development Price Index. BRDPI measures how much the NIH budget must change to maintain same purchasing power.\(^9\)

The CAGR of NIH funding from 1994 to 2003 was 9.8%, versus a foundation and private funds CAGR of 6.0% over the same time period. In addition, NIH funding from 2000 to 2009 increased by a CAGR of 3.9% according to the NIH’s Research Portfolio Online Reporting Tools (RePORT) (http://report.nih.gov/rcdc/categories/), versus 2000-2009 US inflation CAGR of 2.3%, according to www.usinflationcalculator.com. (Table 2)

Table 2: NIH Funding in US Billions (2000-2009)

<table>
<thead>
<tr>
<th>Year</th>
<th>2000</th>
<th>2001</th>
<th>2002</th>
<th>2003</th>
<th>2004</th>
<th>2005</th>
<th>2006</th>
<th>2007</th>
<th>2008</th>
<th>2009</th>
<th>2000-09 CAGR</th>
</tr>
</thead>
<tbody>
<tr>
<td>NIH</td>
<td>$14.8B</td>
<td>$16.8B</td>
<td>$19.1B</td>
<td>$21.9B</td>
<td>$22.9B</td>
<td>$23.4B</td>
<td>$23.2B</td>
<td>$21.3B</td>
<td>$23.5B</td>
<td>$21.7B</td>
<td>3.9%</td>
</tr>
</tbody>
</table>

Foundation funding made up a very small percentage (<5%) of all US biomedical funding. As seen in Table 1, percentage allocations across industry, National Institute of Health (NIH), and other sources remained consistent in the 1994-2003 timeframe, but industry shifted a higher percentage of its resources from pre-clinical, early-stage development to less risky, later-stage
activities. The NIH continues to focus on relatively low-risk basic research that relies on a democratic study section review process for grant funding. The NIH-style of funding was considered the gold standard of grant making in biomedical research until recently. Richard Sprout, former executive director of the Ellison Medical Foundation and ex-director of the National Institute on Aging, has echoed these criticisms of a conservative NIH. When he was at the NIH, he recalls having to contemplate whether he could “live with [the award] on the front page of The Washington Post.” Biomedical foundations still continue to model their basic research grant processes after the NIH.

**Focus on Disease-Focused Foundation (DFF) Activities**

In the past 10 to 20 years, there has been a rise of disease focused foundations (DFF) that are wholly devoted to or have subsidiaries devoted to de-risking promising drug candidates in the drug discovery and development value chain. DFFs focus on a narrow therapeutic scope or orphan diseases with small markets and thus perceived limited market upside. Another targeted area of funding to address perceived market failure has been neglected diseases of poverty such as malaria and tuberculosis. DFFs, in essence, seek to create functioning markets where they perceive the greatest market failures. These failures are usually located in the transition from the academic investigator’s lab to human clinical trials. This phase in the drug discovery and development lifecycle is known as translational research and early-stage development. Pharmaceutical and medical device companies looking to evaluate the financial net present value of potential programs rely on market estimates, total development costs, and robust intellectual property. These players often shied away from investing in markets with a small number of patients, as this effectively capped the number of potential customers and decreased the probability that sales of this product could increase earnings and pass the internal hurdle rate. By de-risking clinical uncertainty and lowering development costs, DFFs have sought to change the equation in their favor.

The premise is that by providing crucial capital during the drug development lifecycle at precisely the point where capital is most scarce, DFFs can move forward the drug/therapy/tool program to the point where it can garner more traditional funding from venture capitalists, large life science companies, or the public markets. For example, the Cystic Fibrosis Foundation made waves with the first and largest DFVP collaboration to date; $46.9M over 5 years to
Aurora Biosciences to screen potential drug candidates for cystic fibrosis in May 2000. Older DFFs have evolved from investigator-initiated research to directing research efforts with the aid of commercial partners. The Juvenile Diabetes Research Foundation, for example, at over 4 decades old is one of the longest running DFFs. They initiated DFVP efforts about 5 years ago and have ramped up outreach efforts to biotech and pharmaceutical companies for future collaborations.

The Gates Foundation is one of the most well-known examples of a foundation deliberately creating markets where it perceives market failure. The Gates Foundation founded the Global Alliance for Vaccines and Immunization (GAVI) program in 1999 with $750M to purchase vaccines and negotiate tricky differential pricing deals between poorer countries and vaccines manufacturers. It is estimated that 80% of Gates Foundation funding is channeled through existing public-private partnerships with a motley crew of players. These include wealthy donors, national governments, national health agencies, UN and WHO agencies, vaccine manufacturers and distributors, etc. The Gates Foundation venture philanthropy model embodies the shift from the foundations dealing with a single class of grantees (e.g. academic investigators), to multiple stakeholders and partners. DFFs engaged in DFVP have started to grapple with the complexities of partnering with not only their traditional grant recipients, but also with high-maintenance donors, motivated patient organizations, the NIH, the FDA and other regulatory bodies, big pharmaceuticals manufacturers, small biotechnology companies, venture capitalists, CROs (clinical research organizations), IP (intellectual property) lawyers, university technology transfer offices, etc.

**Key Questions**

As DFFs and patient groups raised questions as to the lack of any real output from their grants, they began to understand the potential to diversify from a simple NIH-style grant model to one that addressed the market failures in translational research. They identified that there were significant barriers to academic therapeutic discovery and development. The following factors were described by Dr. Mason Freeman, Director of Translational Medicine, at the Massachusetts General Hospital in Boston, Massachusetts.

- Medicinal chemistry not strongly supported in academia
- Expertise in key regulatory, CMC (process chemists, etc.), and toxicology disciplines lacking
- Timelines of academia not focused on patent expirations and speed (loss of sense of urgency)
- Financial costs of development beyond budgets
- Concerns over conflicts of interests dissuade participation
- Promotions/recognition incentives not aligned with drug discovery process (may be less true in academic medical settings and teaching hospitals, and its ilk)
- Financial rewards of drug development not central to academic mission

As DFFs began to understand academic science incentives and constraints, they realized that academic medicine had neither the resources nor incentives to drive drug development past the initial basic discovery phase. Academics were not interested in scaling and manufacturing issues, process developments, quality control, and other rote activities that had to take place before proof of concept trials in animals for a potential IND filing.

However, to our knowledge, no study has rigorously compared the productivity and impact of foundation-funded projects and programs to that of government funded support in the biomedical arena. This would be difficult to understand as most investigators use multiple and diverse sources of funding to finance their laboratories and post-docs. Regardless of the source of funds, the definition of a successful project was for many years rooted in academia. Metrics such as the number of citations (relative to other papers in that field), relative prestige of the publication, prizes and honors awarded from organizations like the National Academic of Sciences (NAS) served as common yardsticks for academic investigators who received the bulk of DFF funding. These metrics mirrored academic career incentives. ³

Foundations like the Howard Hughes Medical Institute (HHMI) that are focused on basic science research continue to measure success by the number of “plaudits won by its scientists” relative to other investigators. HHMI calculated that is investigators were 10x more likely to be elected to NAS and 16x more likely to win a Nobel prize that those funded by NIH. These metrics serve as proxies for the success of foundation funding for cutting-edge research.
This paper seeks to examine the DFF view of the current market failures, how these DFVP programs map to the drug development value chain, and the deal characteristics including sourcing, selection, project governance and control of DFVP deals. We analyze these questions in four general categories:

1. Investment allocation: Where is the DFF currently investing along the drug development value chain?
2. Investment decision-making: How is the DFF sourcing, selecting, and crafting its deals?
3. Investment governance: How is the DFF controlling and governing its investments?
4. Investment value drivers: How does the DFF perceive itself to add value to its investments?

Data and Methods

This paper seeks to analyze the programs and initiatives that disease focused foundations (DFFs) currently use to commercialize technologies, therapies, and tools relevant to their respective diseases and/or therapeutic areas. Additionally, I examined the “nuts and bolts” of how disease focused venture philanthropy (DFVP) is currently being implemented in DFFs. I also look at specific challenges and best practices faced by DFFs in initiating or implementing DFVP. For this analysis, data was gathered from publications, DFF websites, the Faster Cures’ TRAIN (The Center for Accelerating Medical Solutions) Resources section, the financial statements inside DFF annual reports, Harvard Business Publishing cases, and phone interviews with key DFF staff.

Literature searches focused on venture philanthropy and DFVP whenever possible. MIT Library’s Vera database of e-journals was the starting point for all searches. Publications searched included Nature News (Biomedical Philanthropy special section), JAMA, Chronicle of Philanthropy, etc. A Google Scholar search was utilized to locate ancillary articles that could not be found in MIT’s Vera’s database.

2008 and 2009 annual reports of DFFs that were known to be engaged in DFVP were downloaded from each respective foundation’s website and were examined for specific program details. The Harvard Business Publishing (HBP) case on the Cystic Fibrosis Foundation
and its dealings with Vertex Pharmaceuticals during its acquisition of Aurora Biosciences was the paper that germinated this thesis topic. A draft copy of the HBP Myelin Repair Foundation case was utilized as it was being written during spring 2010 for a Harvard Business School MBA class discussion.

Sixteen 1-hr telephone interviews with foundation staff in the following DFFs were conducted between February and April 2010. Foundation staff contacts were provided by Professor Fiona Murray, students in her thesis group, previous relationships, suggestions from other DFFs, and a general Google search. Each interviewee was asked about their background, their roles and responsibilities in their current positions, and different programs and processes that were used in their DFF. Interview notes were written in real-time, and are available from the author.

**DFF Phone Interviews List**

1. Accelerate Brain Cancer Cure Foundation (ABC2)
2. Alzheimer’s Drug Discovery Foundation
3. Bill & Melinda Gates Foundation
4. Christopher Reeve Foundation
5. Cystic Fibrosis Foundation
6. Epilepsy Therapy Project
7. Faster Cures
8. Foundation Fighting Blindness
9. Juvenile Diabetes Research Foundation
10. Leukemia and Lymphoma Society
11. Michael J. Fox Foundation for Parkinson’s Research
12. Multiple Myeloma Research Foundation
13. Muscular Dystrophy Association
14. Myelin Repair Foundation
15. Prostate Cancer Foundation

Interview questions asked included the following:

- Do grant monies from your DFF act as complements or substitutes?
• Does increased NIH funding towards your particular disease decrease or increase private foundation grants?
• Historically, why has your DFF grants not led to a successfully commercialized therapy? Where is the source of the market failure? Or do they address market failures?
• What is the deal structure of your venture philanthropy partnerships (e.g. equity investments, milestone payments, royalty-based, etc.)? What is the governance structure?
• What are hypotheses espoused by your DFF with regards to the problem of funding low-priority charity product development?
• How is your DFF allocating monies and exerting control? How does your DFF perceive themselves to add value (e.g. $, expertise, materials)?
• What incentives exist today for early-stage companies to pursue projects funded by your DFF? How can foundations create the proper structure with regards to market-making, materials, etc?

The report focuses on the well-known DFFs currently practicing on DFVP. There are undoubtedly other DFVP practicing DFFs that have been omitted in the analysis. DFFs that were analyzed in this section were chosen for data availability and accuracy. Any omission is unintentional and should be construed accordingly. Categorizations of the DFVP programs were based on interviews, annual reports, and publically available information. If sufficient information could not be found and/or was requests for information were declined, the categorization was omitted.

The set of DFFs analyzed were as follows.

1. Alzheimer’s Drug Discovery Foundation
2. Christopher Reeve Foundation
3. Cystic Fibrosis Foundation
4. Epilepsy Therapy Project
5. Foundation Fighting Blindness
6. Juvenile Diabetes Research Foundation
7. Leukemia and Lymphoma Society
8. Michael J. Fox Foundation for Parkinson’s Research
9. Multiple Myeloma Research Foundation
10. Myelin Repair Foundation
11. Prostate Cancer Foundation

**Investment Allocation: Where is the DFF currently investing along the drug development value chain?**

The drug discovery and development pathway has been described at length in academic publications, the lay press, business journals, and online. A general description of each significant phase of the process is described below. The specific details of each process will not be described here. A primer written by the Institute for the Study of Aging and Alzheimer Research Forum is available for interested readers at [http://www.alzforum.org/drg/tut/ISOATutorial.pdf](http://www.alzforum.org/drg/tut/ISOATutorial.pdf).

Generally, the drug development pipeline has three major sequential stages: Research, Translational Research, and Clinical Research. Each stage is broken down into a series of smaller processes, as shown below. Basic research, the first stage, is where science and technology is explored by scientists in mostly academic and sometimes corporate settings. Translational research, the second stage, takes the discoveries and advances from basic research and fashions disease models, new targets for therapies, and chemicals aimed at blocking/activating steps in the disease process. Additionally, transitional research encompasses in vivo testing in animals such as mice and dogs. A crucial step in translational research is the tests to understand how this drug candidate might behave in a human being. Once sufficient evidence from animal studies is available, pharmaceutical and biotechnology companies solicit and receive regulatory approval from the FDA to begin human clinical trials. The last phase, clinical research, centers on safety and efficacy of said drug candidate in human beings.

Commercializing a successful drug, that is, going through each and every step of the drug development pathway, has been compared to trying to thread a long string through 10,000 sequential needles. Miss any checkpoint and the program is doomed.

The first phase, basic research, has mostly been in the province of academic researchers. These are the primary investigators (PIs) who run laboratories in universities and research hospitals all
over the world. The vast bulk of their funding is funneled from the US government via the NIH and its member institutes.

Clinical research, the last phase, is performed almost exclusively by for-profit healthcare companies such as pharmaceutical and biotechnology companies. These companies partner with CRO’s (Clinical Research Organizations) to efficiently manage and supervise complex human trials that span multiple centers, geographies, investigators, and years.

The translational research has been identified as the “Valley of Death” as most DFF funded research historically did not make the transition to clinical trials. The reasons have been delineated in the background section regarding the factors that impede academic investigators from successfully translating their scientific discoveries. Additionally, biopharmaceutical companies historically have not had the appetite for licensing therapeutic candidates prior to solid pre-clinical and/or Phase 1 clinical trial data.

**Figure 1: Drug Development Value Chain**
The solid green, and dotted yellow and red lines signal the three general market failure areas of the DFFs analyzed. The green box indicates the historical DFF grant-making focus on investigator-driven basic research. The yellow dotted box indicates the diversification into some or all translational activities. The red dotted box indicates that the DFF is willing to support, at minimum, initial human clinical trials. Note that as the scope of the DFF broadens, the amount of risk capital at stake increases, and the dollars needed to drive development explodes.

To date, few foundations have articulated that they are ready and willing to drive promising programs all the way through registration trials. The DFFs who are actively engaged in later-stage clinical trials correlate with the largest cumulative fund level over their history. General details about the DFVP programs of DFFs profiled here can be found in Appendix A.

**Investment Decision-Making, Governance, and Value Drivers Factors**

Many of the descriptive partnership factors listed below were taken from a 2003 paper by Lerner, Shane, and Tsai that examined biotechnology alliances. Each foundation was assessed across the selected categories using their respective 2008 or 2009 annual reports and through phone interviews. Assessments were made based on partnerships with commercial partners wherever possible.

**Investment Decision-Making: How is the DFF sourcing, selecting, and crafting its deals?**

- Sourcing and Selection:
  - Source of partnership: investigator, company, DFF
  - Selection process: business advisory board, science advisory board, both, none, other
  - Due diligence resources: in-house, outsource, hybrid, etc.
- Deal terms:
  - Financial instruments: Milestone-based payments, return capped at multiple of future sales, equity investments, warrants, other
  - Duration (length of partnership)\(^3\text{5}\)
  - Payment at time of signing/closing\(^3\text{5}\)
  - Min, max, median total grant amounts in US dollars
• Intellectual Property (IP):
  o Ownership of patents generated by partnership: DFF, partner, other
  o March-in/reversion/interruption rights
  o Publications and knowledge sharing

**Investment Governance: How is the DFF controlling and governing its investments?**

• Governance:
  o Frequency of updates: monthly, quarterly, bi-annually, annually, never, other
  o Seat on partner’s board
  o Equity stake w/ associated voting rights
  o Oversight board/committee

• Other control rights:
  o Day to day project management: DFF, partner, both
  o Alterations to scope by extending duration of project, DFF, partner, both
  o Alterations to scope by cancelling partnership: DFF, partner, both

**Investment Value Drivers: How does the DFF perceive itself to add value to its investments?**

• Perceived DFF value drivers:
  o Business strategy
  o Scientific advisors
  o Venture capital

**DFF Categories**

Additionally, each DFF was characterized by the several foundation-level characteristics.

• Source of funds: Few major donors, Large number of donors, Family foundation, Parent organization, other
• DFF years in existence: 0-5, 6-10, 10+ years
• Overall annual fund level: <$25M, $25-50M, $50-100M, $100M+
• Performance metrics used to gauge success
• Number of commercial partners
• Total $$ spent on for-profit grants
• Spun-out companies
• Organize conferences to bring multiple stakeholders together

The scope of the paper encompasses US-based, private-public partnerships between disease-specific non-profit organizations (or DFFs) and industry (biotech, pharma, CEOs, anyone in the for-profit biomedical ecosystem). These were public charities who received financial support from the public, wealthy individuals, and other foundations as defined by IRS section 501(c)(3). Entities outside of the scope include medical research organizations such as the UK's Wellcome Trust or Howard Hughes Medical Institute (HHMI), health delivery services organizations, government funding organizations (e.g. NIH, any institute under the NIH), non-life science and non-medical organizations.

Results and Analysis

Investment Allocation: Map of DFVP Programs
Figure 2: Map of DFVP Programs across Drug Development Value Chain
The DFFs mapped to 4 different groups with increasing scope. Three DFFs in Group 1 spanned the entire continuum from basic research to Phase 3 registration trials; four DFFs in Group 2 funded up until proof of concept Phase 2 trials; 3 DFFs in Group 3 focused up until Phase 1 safety trials, and 1 DFF in Group 4 stayed exclusively in the translational research and preclinical validation space.

The Alzheimer’s Drug Discovery Foundation (ADDF), Cystic Fibrosis Foundation (CFF), and Juvenile Diabetes Research Foundation (JDRF), are the 3 DFFs in Group 1 with the broadest funding scope. These 3 DFFs are amongst the longest years in existence, and have more detailed performance scorecards to assess historical performance and inform future investments. For example, ADDF looked at how far any particular project progressed per ADDF dollar spent and the amount of follow-on funding. CFF created a point scoring system to judge overall pipeline progress for a bottoms-up approach, and complemented this with a top-down life expectancy measure. JDRF laid out 6 strategic therapeutic objectives, and measured each project against whether it advanced any of these goals.

It is interesting to note that as the public markets and venture capitalists have shifted away from pre-clinical compounds with long investment horizons, DFFs like the Cystic Fibrosis Foundation and Leukemia and Lymphoma Society have had to broaden their de-risking activities. It was originally postulated that a DFF would need to fund up to Phase I at the latest before another partner would come in for the “handoff” to take it through later stage clinical trials. It has become clearer that this is no longer the case. Future developers are asking for more Phase II and even Phase III trials before they license the program in question. Thus, the market failure being addressed by DFFs continues to shift and broaden to downstream drug development.

The Foundation Fighting Blindness (FFB), Multiple Myeloma Research Foundation (MMRF), Leukemia and Lymphoma Society (LLS), and Michael J. Fox Foundation for Parkinson’s Research (MJFF) in Group 2 all sponsored projects up to Phase 2 trials. All of these DFFs had large cumulative fund levels in excess of $100+ over the DFF’s existence. These DFFs felt that their current resources were insufficient to fund large scale Phase 3 trials, and were all actively sought positive, ongoing relationships with industry heavyweights to ensue projects funded up to Phase 2 did not fall off a cliff.
Within each DFF, annual priority-setting sessions would dictate portfolio optimization. For example, the Foundation Fighting Blindness chose NOT to fund wet macular degeneration projects because that was considered to be commercially well-funded. It decided instead to focus on markets that lacked capital, such as inheritable retinal diseases.

The Epilepsy Therapy Project (ETP), Prostate Cancer Foundation (PCF), and Christopher & Dana Reeve Foundation were the 3 DFFs in Group 3 who were comfortable making grants up until Phase 1 human safety trials. This was a strategic decision on the part of ETP and PCF to focus their efforts on the translational phases of drug development. They felt that the scientific understanding of their disease was at a stage where better animal models and clinically validated tools needed further development vs. pushing potential therapies into clinical trials. A note about the Christopher & Dana Reeve Foundation: they have made one-off DFVP investments, but are still planning a more cohesive DFVP rollout, and thus do not have a formalized DFVP program.

Finally, the Myelin Repair Foundation (MRF), a DFF looking to cure multiple sclerosis, in Group 4 focused exclusively on target identification projects. As a DFF with relatively less funds vis-à-vis the older, more established DFFs, the MRF is taking a step-wise approach by choosing to stay in a narrower band of drug development.

The minimum, maximum, and mean deal amounts did not correlate to where any particular group. For example, Group 1 had ADDF at one end of the spectrum with relatively small bets with mean amounts of $600k, whereas JDRF made relatively larger deals with means of $2M per partnership. On the similar note, Group 2’s Leukemia and Lymphoma Society made fewer number of grants with larger amounts up to a maximum of $3.7M per deal, but the Multiple Myeloma Research Foundation signed more deals with less given per deal and a maximum of $1.5M. The DFFs in Group 3, with less emphasis on human clinical trials than Groups 1 & 2, logically spend less per deal with have lower maximum amounts as well.
## Investment Decision-Making: Sourcing and Selection

### Table 3: Sourcing & Selection Categorization of Interviewed DFFs

<table>
<thead>
<tr>
<th>#</th>
<th>Sourcing &amp; Selection</th>
<th>Source of Partnership: Investigator, Company, DFF</th>
<th>Selection Process: Business Advisory Board, Science Advisory Board, Both</th>
<th>Due Diligence Resources: In-house, Outsource, Hybrid</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Alzheimer's Drug Discovery Foundation / Institute for the Study of Aging(^{23,25})</td>
<td>Investigator, Company, DFF</td>
<td>Both</td>
<td>Hybrid</td>
</tr>
<tr>
<td>2</td>
<td>Christopher &amp; Dana Reeve Foundation(^{19})</td>
<td>Investigator, Company</td>
<td>Science Advisory Board</td>
<td>Outsource</td>
</tr>
<tr>
<td>3</td>
<td>Cystic Fibrosis Foundation(^{21,30,36})</td>
<td>Investigator, Company, DFF</td>
<td>Both</td>
<td>Hybrid</td>
</tr>
<tr>
<td>4</td>
<td>Epilepsy Therapy Project(^{28})</td>
<td>Investigator, Company, DFF</td>
<td>Both</td>
<td>Hybrid</td>
</tr>
<tr>
<td>5</td>
<td>Foundation Fighting Blindness(^{38})</td>
<td>Company, DFF</td>
<td>Both</td>
<td>Outsource</td>
</tr>
<tr>
<td>6</td>
<td>Juvenile Diabetes Research Foundation (JDRF)(^{27,29})</td>
<td>Investigator, Company, DFF</td>
<td>Both</td>
<td>Hybrid</td>
</tr>
<tr>
<td>7</td>
<td>The Leukemia &amp; Lymphoma Society(^{33})</td>
<td>Investigator, Company, DFF</td>
<td>Both</td>
<td>Hybrid</td>
</tr>
<tr>
<td>8</td>
<td>Michael J. Fox Foundation for Parkinson's Research(^{37})</td>
<td>Investigator, Company, DFF</td>
<td>Both</td>
<td>Hybrid</td>
</tr>
<tr>
<td>9</td>
<td>Multiple Myeloma Research Foundation(^{32})</td>
<td>Investigator, Company, DFF</td>
<td>Both</td>
<td>In-house</td>
</tr>
<tr>
<td>10</td>
<td>Myelin Repair Foundation(^{24})</td>
<td>Investigator, DFF</td>
<td>Both</td>
<td>Outsource</td>
</tr>
<tr>
<td>11</td>
<td>Prostate Cancer Foundation(^{31})</td>
<td>Investigator, Company</td>
<td>Both</td>
<td>Outsource</td>
</tr>
</tbody>
</table>

Most DFFs had multiple sources of partnerships: investigator, company, and internally. In many cases, the DFF was approached by companies looking for potential partnerships. The only DFF that did not have companies as the primary source of deals was the Myelin Repair Foundation, which was a function of the MRF's narrow focus on target identification activities. As DFFs began to build name recognition and scientific credibility within industry, this led to a virtuous cycle where companies would regularly solicit the DFF for funds. When a DFF first launched a DFVP program, it would identify tangible rewards to incentivize industry cooperation. For example, when JDRF first rolled out its Industry Discovery & Development Partnerships (IDDP) Program, there was much more "push" from JDRF than "pull" from potential commercial collaborators. As the IDDP program got underway, the "pull" from potential partners became much greater than its marketing efforts, and it found that most firms interested in the juvenile diabetes space.
proactively contacted JDRF. In 10 of the 11 DFFs interviewed, academic collaborators played matchmaker by bringing a small company to the attention of the DFF, albeit with rarer frequency.

DFFs also frequently engaged in annual gap analysis sessions to help identify, clarify, or update both long-term and short-term priorities. The Gates Foundation is known for bringing all the players to one table to brainstorm if it does not feel comfortable with its current grasp of the state of affairs. And according to Peter Lomedico, JDRF’s Director of Strategic Alliances and Industry Partnerships, JDRF also performs formal gap analysis exercises to categorize particular problem statements as a funding, science, or regulatory gap. Areas of opportunities for future investments were outputs of these sessions. Requests for applications were often categorized under the designated priority areas to help chart and track project progress and ensure a balanced portfolio. The portfolio rebalancing review helped account for attrition of old projects and offsets by new projects. Dr. Diana Wetmore, VP of Alliance Management at the Cystic Fibrosis Foundation, explained that the portfolio approach necessitates “more shots on goal”. Thus it was essential that CFF systematically reviewed its current “shots” in play to see if there were holes that needed to be plugged.

All DFFs with formal DFVP programs that were analyzed for this report used both a scientific and business advisory committee. During the project selection process, the first step after receipt was to have a scientific advisory committee review and vet the scientific risk and robustness of the proposal. Larger DFFs like the JDRF have in-house research departments that complement external scientific advisors to identify opportunities, participate in funding recommendations, and manage relationships. If the proposal passed this step, it was then assessed by an independent business advisory group. The group is often comprised of venture capitalists, industry professionals from pharmaceutical and biotech companies, and entrepreneurs, and is also heavily populated with members from the DFF’s Board of Directors. The due diligence was usually validated by external consultants, guided by foundation staff. For example, Ernst & Young was hired by one DFF to conduct independent audits of potential partners during the information validation stage of due diligence efforts.
For potential partnerships with small, private partners, DFFs often took an extra step of ensuring financial solvency for any number of years (e.g. 2-3 years) following the project. Dr. Louise Perkins of the Multiple Myeloma Research Foundation remarked that “2 years” of funding was needed for the MMRF to get comfortable making an investment. She also added that even over the course of a few months of negotiations, the finances of smaller companies can change materially, so it was imperative to receive frequently updated financials from potential partners. Dr. Steve Rose, Chief Research Officer of Foundation Fighting Blindness, clarified that when companies seeking non-dilutive capital from FFB had to simultaneously submit a business plan and a scientific proposal. Taking the extra step assuages fears of running out of cash, especially for smaller, less-established foundations like FFB and Accelerate Brain Cancer Cure (ABC2) that do not have the deeper pockets of more established DFFs. Depending on the project scope and grant amount, the DFF’s Board of Directors might be needed at the final approval stage. Dr. Jonathan Simons, President and CEO of the Prostate Cancer Foundation, even commented that PCF was “not that different from a venture capital fund” in its operations.

In all cases, there was ongoing dialogue between the potential partner and the DFF to negotiate the milestones and payment schedules and IP, as well as clarification of scientific, technical, and clinical risks. In addition, DFFs often acted quickly once the contract was signed to accelerate the learning curves of companies unfamiliar with their particular indication by educating them on current tools, scientific difficulties faced in the past, etc.

**Investment Decision-Making: Deal structure and deal terms**
### Table 4: Deal Terms Categorization of Interviewed DFFs

<table>
<thead>
<tr>
<th>Deal Terms</th>
<th>Financial Instruments:</th>
<th>Duration: (length of partnership)</th>
<th>Payment at time of signing / closing:</th>
<th>Min, max, mean total grant amounts in US dollars</th>
<th>Company matching funds</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alzheimer's Drug Discovery Foundation / Institute for the Study of Aging11,15</td>
<td>Convertible notes, milestone-based payments, warrants, royalties with cap as multiple on investments</td>
<td>1 yr + option for follow-on funding</td>
<td>Yes</td>
<td>(1998-2006) Min: $10k, Max: $600k, Mean: $174k</td>
<td>Varies</td>
</tr>
<tr>
<td>Christopher &amp; Dana Reeve Foundation24</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>Cystic Fibrosis Foundation15,30, 16</td>
<td>Milestone-based payments, royalties with cap as multiple on investments</td>
<td>Varies, starts at 2 yrs</td>
<td>Yes</td>
<td>$200k/yr (pre-clinical), $750k/yr (clinical)</td>
<td>Yes</td>
</tr>
<tr>
<td>Epilepsy Therapy Project28</td>
<td>Milestone-based payments, equity investments</td>
<td>1 yr + option on 2nd yr</td>
<td>Yes</td>
<td>Min: $5k, Max: $200k, Mean: $100k</td>
<td>Yes (50%)</td>
</tr>
<tr>
<td>Foundation Fighting Blindness28</td>
<td>Milestone-based payments, equity investments</td>
<td>Varies</td>
<td>Yes</td>
<td>Unknown, but 1st collaboration w/ Oxford Biomedica ~$3M</td>
<td>N/A</td>
</tr>
<tr>
<td>Juvenile Diabetes Research Foundation (JDRF)17,29</td>
<td>Milestone-based payments, equity (TolerX), royalties with cap as multiple on investments</td>
<td>2-3 yrs, option on 3+ yrs</td>
<td>Yes</td>
<td>Min: $200k, Max: $5M, Mean: $2M</td>
<td>Yes (50-50)</td>
</tr>
<tr>
<td>The Leukemia &amp; Lymphoma Society8</td>
<td>Milestone-based payments, equity, warrants, royalties with cap as multiple of investments</td>
<td>2-3 yrs</td>
<td>Yes</td>
<td>Max: $3.7M</td>
<td>Yes</td>
</tr>
<tr>
<td>Michael J. Fox Foundation for Parkinson’s Research27</td>
<td>Milestone-based payments; royalties with cap as multiple of investments</td>
<td>2 yrs</td>
<td>Yes</td>
<td>N/A</td>
<td>No</td>
</tr>
<tr>
<td>Multiple Myeloma Research Foundation12</td>
<td>Milestone-based payments, royalties with cap as multiple</td>
<td>2 yrs</td>
<td>Yes</td>
<td>Min: $50.9M, Max: $1.9M, Mean: $1M</td>
<td>Yes (varies)</td>
</tr>
<tr>
<td>Myelin Repair Foundation24</td>
<td>Milestone-based payments</td>
<td>1 yr + option on 2nd yr</td>
<td>Yes</td>
<td>N/A</td>
<td>No</td>
</tr>
<tr>
<td>Prostate Cancer Foundation21</td>
<td>N/A</td>
<td>Varies by program</td>
<td>Yes</td>
<td>$300k to $1M</td>
<td>No</td>
</tr>
</tbody>
</table>

The most widely used investment facility was the milestone-driven grant. In the analysis, every DFF engaged in DFVP (10 out of the 11 interviewed) utilized the milestone-driven grant as their primary means of DFVP grant-making. This structure takes its cues from the tranches of VC monies from a financing series and is comprised of an upfront payment plus one or more subsequent payouts contingent on timeline-driven milestones and deliverables. For example, the Multiple Myeloma Research Foundation, like most other DFFs, utilized clinical significant goalposts for follow-on payouts such as: procurement of clinical grade drug substance for clinical trial, initiation of pre-clinical animal studies, first patient first visit, last patient last visit. For pre-Phase I partnerships, initiation and completion of discrete bands of activities such as animal toxicology studies were often utilized.
Options, warrants, and other more sophisticated investment vehicles are used much less frequently. The only two DFFs that utilized financial instruments outside of milestone-based payments and equity capital were the Alzheimer’s Drug Discovery Foundation and the Leukemia & Lymphoma Society. They both used hybrid securities like convertible notes and warrants to protect their downside with a steady cash flow and keep an option on the upside by converting to equity. Interviews with DFF staff suggested that the need for more creative financial models, especially for DFFs who go beyond the translational space to the clinical space. It was clear that the “comfort zone” of DFFs remained squarely within the milestone-based regimen. A reticence to use more complicated financial investment tools may stem, especially from DFFs in Groups 1 and 2, from a fear of being perceived as too focused on the financial return of potential investments and thus unseemly.

Equity was used with extreme caution by most DFFs. It was not ruled out as an option, but there was a general consensus that equity investments should be made sparingly. Less than half or 4 out of the 11 DFFs utilizing equity investments as a investment vehicles. The Epilepsy Therapy Project has made small equity investments in 5 companies, while the Leukemia & Lymphoma Society have declared that equity investments are possible, but has chosen not to do it yet. Representatives from both DFFs claim that equity is an option, but were still adjusting their mindsets to embrace higher risks equity vs. lower risk milestone-based payment structures. JDRF has made 1 equity investment out of 33 deals to date. TolerRx, a Boston-based immunology company, raised $35M in a Series C round. JDRF invested $3.5M on the same deal terms as the other venture capitalists and institutional investors in the syndicate.

A key disincentive for public DFFs to shy away from equity investments is how these investments will show up on charity rating sites. If a DFF chose to take equity, it would have to list it on their balance sheets as an asset and conduct yearly valuations. If these equity investments “failed”, the DFF would need to write down that asset, depressing their balance sheet and subsequent ratings by outside charity evaluators like Charity Navigator. This would discourage would-be donors from contributing.
In addition, US Securities Act of 1933 defines an accredited investor as “any organization described in section 501(c)(3) of the Internal Revenue Code, corporation, Massachusetts or similar business trust, or partnership, not formed for the specific purpose of acquiring the securities offered, with total assets in excess of $5,000,000.” A public DFF without an endowment, like the Accelerate Brain Cancer Cure (ABC²) foundation, would most likely have less than $5M in total assets and therefore unable to transact equity investments.

The duration of most deals starts at 1 to 2 years, and is coupled with an option to extend should both parties see fit. Three DFFs, ADDF, Epilepsy Therapy Project, and Myelin Repair Foundation, started with 1 yr partnerships, with an option to continue into the 2nd year if the negotiated milestone during the 1st year were met. Four other DFFs, including CFF, JDRF, LLS, MJFF, and MMRF, started with 2 year contracts that, depending on the project scope, could be extended if necessary. Note that these 4 DFFs are all in Groups 1 or 2. It makes sense that DFFs whose purview encompasses Phase 2/3 trials have longer initial durations, since the time to plan, execute, and produce data from a human trial is often longer than that of a pre-clinical animal study. Two DFFs, Foundation Fighting Blindness and the Prostate Cancer Foundation, did not have default project durations, choosing to customize each deal as they saw fit.

There are very rarely “penalties”, financial or otherwise, for companies that fail to meet the milestones during the life of the partnership. None of the DFFs interviewed indicated that their commercial partners were liable for any financial damages if milestones were not met. The sentiment expressed by Rusty Bromley at the Myelin Repair Foundation was representative of the power asymmetry most DFFs felt, “Command and control doesn’t work. Coercing and cajoling does.” However, DFVP program directors brought up a DFVP meme of DFVP investments as value-creating steps for both parties: the company can bring in non-dilutive capital and produce value-inflected results (e.g. drug program passes animal toxicology studies), the DFF can show a link between their investment and progress towards therapy commercialization. A March 29, 2010 press release by Avila Therapeutics “Avila Teams with Leukemia Society”, is classic example of how a commercial partner (Avila) announces a large investment ($3.2M) by a DFF (Leukemia & Lymphoma Society) to support a disease-focused therapy (knocking out Btk in B-cell development thus reducing B-cell related cancers). Both commercial and DFF partners “win”.

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Six out of the eleven DFFs also require royalties as a potential return on their investments. It was widely acknowledged that DFVP investments were and are not made for the purposes of a high financial return. As Dr. Joyce Cramer of the Epilepsy Therapy Project remarked, “When we give money to an early stage company, the legal fees are high enough that we’re not going to make money out of it. There’s no expectation of ever seeing a nickel come back to us.” Nevertheless, it is thought that a token “fair return” is appropriate as a trade-off for the non-dilutive nature of the risk capital provided. Ultimately, DFFs want to capture any potential upside and funnel these returns back into additional DFVP investments. Royalties hover around the low single digits, and are usually capped between 2 to 6x multiple of the original DFVP investment. For example, JDRF uses 3-4x and the Foundation Fighting Blindness uses 2-3x. The Leukemia and Lymphoma Society uses a stepwise multiples model where the initial approval in a major market, such as US or Japan, triggers a 1x return on investment. Additional multiples are sales are rolled out are capped at 2-4x. A modest payback to the foundation based on the commercial success of the program is thought to be more symbolic than fiscal as most projects would have negative present values. These arrangements are usually also made applicable to any sublicensing agreements that the commercial partner may choose to engage in.43

All DFFs with formal DFVP programs, with the notable exception of the Michael J. Fox Foundation for Parkinson’s Research, Myelin Repair Foundation and the Prostate Cancer Foundation, require matching company funds. It is thought that companies need to show tangible commitment by putting “skin in the game”, analogous to prospective investors wanting to see company founders put some of their personal wealth on the line. The matching percentage varies, but most hover around 50% (also known as 1:1 matching grants). Both the Epilepsy Therapy Project and JDRF required 1:1 matching funds, while ADDF, CFF, LLS, MMRF vary their match requirements. The logic to incent the company by requiring internal cash use is coupled with the lack of financial penalties to create a stronger incentive for successful project completion.

**Investment Decision-Making: Intellectual Property**

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Table 5: Intellectual Property (IP) Categorization of Interviewed DFFs

<table>
<thead>
<tr>
<th>#</th>
<th>Intellectual Property (IP)</th>
<th>Ownership of patents generated by partnership:</th>
<th>March-in / walk-in rights / reversion / interruption clauses</th>
<th>Publications and knowledge sharing</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Alzheimer’s Drug Discovery Foundation / Institute for the Study of Aging</td>
<td>Partner</td>
<td>Varies</td>
<td>Yes</td>
</tr>
<tr>
<td>2</td>
<td>Christopher &amp; Dana Reeve Foundation</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>3</td>
<td>Cystic Fibrosis Foundation</td>
<td>Partner</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>4</td>
<td>Epilepsy Therapy Project</td>
<td>Partner</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>5</td>
<td>Foundation Fighting Blindness</td>
<td>Partner</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>6</td>
<td>Juvenile Diabetes Research Foundation (JDRF)</td>
<td>Partner</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>7</td>
<td>The Leukemia &amp; Lymphoma Society</td>
<td>Partner</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>8</td>
<td>Michael J. Fox Foundation for Parkinson’s Research</td>
<td>Partner</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>9</td>
<td>Multiple Myeloma Research Foundation</td>
<td>Partner</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>10</td>
<td>Myelin Repair Foundation</td>
<td>Partner</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>11</td>
<td>Prostate Cancer Foundation</td>
<td>Partner</td>
<td>N/A</td>
<td>Yes</td>
</tr>
</tbody>
</table>

To encourage the commercial partner to accelerate project development, the intellectual property in question always resided with the partner in the 10 DFFs with formal DFVP programs, not with the DFF. Additionally, IP generated in the duration of the project (e.g. process claims, know how, etc.) are considered to be under the partner’s control. Phone interviews suggested that IP was an area that DFFs considered outside of their area of expertise, and was often delegated to legal counsel or outside IP attorneys. (One noted exception was the Multiple Myeloma Research Foundation. It hired in-house counsel to reduce inefficiencies in the contract negotiation process.) Nevertheless, it was felt that as a business necessity, foundation staff needed to understand the IP landscape from a commercially-attractive therapeutic perspective. Paraphrasing Dr. Diana Wetmore of the Cystic Fibrosis Foundation, without the “philanthropy”, companies would not pick our patients to work with. Without the “venture”, companies would not be able to find a revenue stream that is attractive. And IP was the bedrock of future revenue and freedom to operate.

However, every DFF engaged in DFVP, with the notable exception of the Myelin Repair Foundation, has a version of what Schaner & Lubitz, PLLC calls an “interruption license.”

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Alternatively called “march-in”, “walk-in”, or “reversion” rights, an interruption license protects
the project from being abandoned prior to completion due to business reasons, also called an
“interruption event”. An interruption event can be broadly defined as “a cessation of reasonable
efforts to develop a commercial product from the intellectual property over an extended
period.”\textsuperscript{44} These “bring back” clauses give the DFFs the right, if the company decides to halt
development for financial reasons or the company goes under, to come in, take the asset with
process know-how knowledge, and find another development partner. Should this clause be
triggered, the IP and scientific know-how would be transferred to the DFF to sub-license as it
sees fit.\textsuperscript{36} It is now considered standard best practice to include these IP clauses into the
contract as the absolute dollar amounts in DFVP awards increases and are “sufficiently large
that waste can be devastating”.\textsuperscript{44}

Although the triggering of an interruption license is an unfortunate event, it has occurred due to
financial insolvency. For example, the Cystic Fibrosis Foundation has had two workout situations
in the past year alone. Both Epix Pharmaceuticals and Altus Pharmaceuticals had insufficient
capital to operate as a going concern, and CFF had to invoke its rights to shop the IP around to
another potential licensor. Altus Pharmaceuticals was unable to continue clinical development
of a partnered program for CFF due to insufficient funds last year. Altus had actually tried to
sub-license the Trizytek program to another potential partner, but was unsuccessful because of
the current recession. CFF ended up organizing the transfer and turnover of the IP from Altus to
Alnara Pharmaceuticals, whose President and CEO had previously served as the Chief Scientific
Officer at Altus. CFF signed a sublicense agreement with Alnara whereby CFF contributed extra
funds to complete the ongoing clinical trials. This extra incentive gave Alnara the push to
cooperate with the IP transfer and perhaps refer their soon-to-be terminated employees to
Altus.\textsuperscript{44}

A frequently vocalized thorny problem was that of technology transfer offices in academic
institutions, and their apparent unwillingness to use the DFF as a broker to out-license IP. A
common problem is misunderstandings amongst the university or academic medical center
(AMC) that holds the IP, the DFF that would rather it be licensed for prospective therapies, and
the industry partner who wants robust IP to protect from competitive infringement. For
example, the Christopher & Dana Reeve Foundation had made a large award to an academic
investigator at Yale University. A biotech was involved with the R&D efforts. Yale’s technology
transfer offices were "dragging their feet", so the foundation began to deduct legal fees from the PI award. Other DFFs have found it challenging to convince the tech transfer offices that they are "trying to give it away”.

**Figure 3: Typical IP Model of Interaction between DFF, Academic Institution, and Commercial Partner**

From a knowledge sharing perspective, partners were often required to share data with the DFF during interim checkpoints. Disclosure requirements range from sharing data with the DFF to open publication of results. The DFFs pooled results from various projects to create an informal central knowledge management system, but commercial partners rarely directly shared information with each other except for published data.

There was an acknowledgment by various DFFs that there needed to be a consensus around IP that maximized collaboration in research, with an IP regime that favored "collaboration over exclusivity." To that end, there has been a concerted push to develop common tools that would allow for sharing of data (e.g. patient record databases, animal models), and to standardize much of the IP terms similar to standardized funding documents.
For the most part, commercial partners maintain an extraordinary amount of control over the program. The DFF is kept in the loop regarding project progress and is called-in for problem solving, but the partner controls the flow of information, the day-to-day operations, and the intellectual property of the program. The ultimate lever that DFFs can exercise is the financial commitment. In the past, DFFs have terminated or suspended projects mid-stream because of non-progress. In these cases, more sophisticated DFFs like the CFF have arbitration clauses to resolve conflicts over changes to project scope.

Table 6: Governance Categorization of Interviewed DFFs

<table>
<thead>
<tr>
<th>No.</th>
<th>Governance</th>
<th>Frequency of updates:</th>
<th>Seat on partner's board</th>
<th>Equity stake w/ associated voting rights</th>
<th>Oversight board / committee</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Alzheimer’s Drug Discovery Foundation / Institute for the Study of Aging</td>
<td>Bi-annually</td>
<td>No (observer rights)</td>
<td>Yes (public partners)</td>
<td>No</td>
</tr>
<tr>
<td>2</td>
<td>Christopher &amp; Dana Reeve Foundation</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>3</td>
<td>Cystic Fibrosis Foundation</td>
<td>Quarterly, Annually</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>4</td>
<td>Epilepsy Therapy Project</td>
<td>Annual</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>5</td>
<td>Foundation Fighting Blindness</td>
<td>N/A</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>6</td>
<td>Juvenile Diabetes Research Foundation (JDRF)</td>
<td>Quarterly</td>
<td>No</td>
<td>Yes (TolerX)</td>
<td>Yes</td>
</tr>
<tr>
<td>7</td>
<td>The Leukemia &amp; Lymphoma Society</td>
<td>Quarterly</td>
<td>No</td>
<td>Yes (Possible, but not yet)</td>
<td>Yes</td>
</tr>
<tr>
<td>8</td>
<td>Michael J. Fox Foundation for Parkinson’s Research</td>
<td>Bi-annually</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>9</td>
<td>Multiple Myeloma Research Foundation</td>
<td>Quarterly</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>10</td>
<td>Myelin Repair Foundation</td>
<td>N/A</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>11</td>
<td>Prostate Cancer Foundation</td>
<td>N/A</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
</tr>
</tbody>
</table>

The frequency of updates and information sharing varied from monthly to annually. Many DFFs employed a two-tier structure of updates: a more formal, face to face update every 6 to 12 months, and an informal, conference call every 1 to 4 months. Four of the 11 DFFs interviewed had at least quarterly updates, while 2 had bi-annual touchpoints. These update meetings involved a combination of updates, identifying bottlenecks and other rate-limiting factors, and creating action plans to ensure critical path risks were mitigated. Some DFFs approached these
meetings as problem-solving opportunities, while others choose to let the partner control the communication updates.

All 11 DFFs surveyed preferred not to take a seat on their partner’s board, even if they had equity stakes with voting rights in the commercial partner (e.g. JDRF for TolerX). Instead, every DFF, with the exception of ADDF and MRF, there was some semblance of an oversight committee co-led by a DFF project manager. This oversight board was utilized during update meetings to tackle critical path items, reassess risk, and report back to their respective constituencies on project progress. In CFF, for example, the makeup of the oversight board, also known as a steering committee, was made up of equal parts DFF scientific advisors and partner management/scientists. The DFF program manager usually facilitated agenda setting. Similarly, each partnership that LLS establishes has a Research Advisory Committee that is comprised of members from the LLS staff, external scientists and clinicians, and company employees to review progress and anticipate critical path issues on a quarterly basis.

Table 7: Other Control Rights Categorization of Interviewed DFFs

<table>
<thead>
<tr>
<th></th>
<th>Other Control Rights</th>
<th>Day to day project mgmt: DFF, Partner, Both</th>
<th>Alterations to scope by extending project duration: DFF, Partner, Both</th>
<th>Alterations to scope by cancelling partnership: DFF, Partner, Both</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Alzheimer’s Drug Discovery Foundation / Institute for the Study of Aging</td>
<td>Partner</td>
<td>Both</td>
<td>Both</td>
</tr>
<tr>
<td>2</td>
<td>Christopher &amp; Dana Reeve Foundation</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>3</td>
<td>Cystic Fibrosis Foundation</td>
<td>Partner</td>
<td>Both</td>
<td>DFF</td>
</tr>
<tr>
<td>4</td>
<td>Epilepsy Therapy Project</td>
<td>Partner</td>
<td>Partner</td>
<td>Both</td>
</tr>
<tr>
<td>5</td>
<td>Foundation Fighting Blindness</td>
<td>Partner</td>
<td>Both</td>
<td>Both</td>
</tr>
<tr>
<td>6</td>
<td>Juvenile Diabetes Research Foundation (JDRF)</td>
<td>Partner</td>
<td>Both</td>
<td>Both</td>
</tr>
<tr>
<td>7</td>
<td>The Leukemia &amp; Lymphoma Society</td>
<td>Partner</td>
<td>Both</td>
<td>Both</td>
</tr>
<tr>
<td>8</td>
<td>Michael J. Fox Foundation for Parkinson’s Research</td>
<td>Both</td>
<td>Both</td>
<td>Both</td>
</tr>
<tr>
<td>9</td>
<td>Multiple Myeloma Research Foundation</td>
<td>Partner</td>
<td>Both</td>
<td>Both</td>
</tr>
<tr>
<td>10</td>
<td>Myelin Repair Foundation</td>
<td>Partner</td>
<td>Both</td>
<td>Both</td>
</tr>
<tr>
<td>11</td>
<td>Prostate Cancer Foundation</td>
<td>Partner</td>
<td>Both</td>
<td>Both</td>
</tr>
</tbody>
</table>

The day to day project operations were almost always managed by the partner. One noticeable exception was ABC2 (not included in above analysis due to lack of information). Dr. David Sandak, VP of Operations for Entrepreneurial Programs, indicated that his DFF steps into the
project manager’s role if there are multiple stakeholders to coordinate, align, and manage. The MMRF’s Multiple Myeloma Research Consortium, a tissue bank consortium of 14 academic medical centers, had an interesting project management where industry-style coordinators were employed by their particular institution, but were paid by MMRC. Part of Dr. Sohini Chowdoby’s role as Associate Director and Team Leader at JDRF is to manage the project within the pipeline programs that are launched each year, reflecting JDRF’s more hands-on approach to project management vis-à-vis that of the other DFFs surveyed. Alterations to scope by extending or cancelling the project usually could be initiated by either party in 9 out of the 11 DFFs analyzed, but it is important to note that the dormant interruption clause discussed in the previous sub-section springs to life if an “interruption event” is deemed to have occurred.

Table 8: Perceived DFF Value Drivers of Interviewed DFFs

<table>
<thead>
<tr>
<th>Perceived DFF Value Drivers</th>
<th>Business Strategy Assistance</th>
<th>Scientific Advisors Access</th>
<th>Venture Capital Connections</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Alzheimer’s Drug Discovery Foundation / Institute for the Study of Aging</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>2. Christopher &amp; Dana Reeve Foundation</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>3. Cystic Fibrosis Foundation</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>4. Epilepsy Therapy Project</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>5. Foundation Fighting Blindness</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>6. Juvenile Diabetes Research Foundation (JDRF)</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>7. The Leukemia &amp; Lymphoma Society</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>8. Michael J. Fox Foundation for Parkinson’s Research</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>9. Multiple Myeloma Research Foundation</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>10. Myelin Repair Foundation</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>11. Prostate Cancer Foundation</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
</tbody>
</table>

DFFs all offered non-value assistance in the form of business strategy advice, scientific advisor access, or venture capital connections. The most common driver was access to external scientists and experts in the field, with all DFFs with formal DFVP programs offering access and introductions to KOLs. Second was venture capital connections, with 8 out of the 11 DFFs analyzed claiming to assist in connecting their commercial partners with venture capitalists, usually those who sat on the DFF’s Board of Directors. The least common driver was identified to be strategic business assistance, with 6 of the 11 DFFs offering some form of business help (e.g. pro bono consultants, etc.) to their commercial partners.
Quick Note on Performance Metrics

Table 9: Performance Metrics of Interviewed DFFs

<table>
<thead>
<tr>
<th>Perceived DFF Value Drivers</th>
<th>Performance Metrics used to Gauge Success</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Alzheimer’s Drug Discovery Foundation / Institute for the Study of Aging^{21,25}</td>
<td>1. Ratio of movement through stages through drug development per $ invested, 2. IP creation per # of programs, 3. External follow-on funding per $ invested</td>
</tr>
<tr>
<td>2. Christopher &amp; Dana Reeve Foundation^{19}</td>
<td>N/A</td>
</tr>
<tr>
<td>3. Cystic Fibrosis Foundation^{15,30,16}</td>
<td>Point system for projects progress to measure overall pipeline; Measuring increases in median life expectancy</td>
</tr>
<tr>
<td>4. Epilepsy Therapy Project^{28}</td>
<td>Number of grants funded (pipeline)</td>
</tr>
<tr>
<td>5. Foundation Fighting Blindness^{28}</td>
<td>N/A</td>
</tr>
<tr>
<td>6. Juvenile Diabetes Research Foundation (JDRF)^{27,29}</td>
<td>Progress against the 6 strategic therapeutic objectives</td>
</tr>
<tr>
<td>7. The Leukemia &amp; Lymphoma Society^{33}</td>
<td>Measuring increases in life expectancy (survival rates) &amp; quality of life</td>
</tr>
<tr>
<td>8. Michael J. Fox Foundation for Parkinson’s Research^{37}</td>
<td>Point-based scoring system, amount of information gleaned, amount of follow-on funding</td>
</tr>
<tr>
<td>9. Multiple Myeloma Research Foundation^{32}</td>
<td>Decreasing cycle time from final protocol to first patient enrolled</td>
</tr>
<tr>
<td>10. Myelin Repair Foundation^{24}</td>
<td>1. Progress against strategic plan to identify &amp; validate myelin repair targets, 2. Identify corporate partner(s), 3. Program progress through drug development</td>
</tr>
<tr>
<td>11. Prostate Cancer Foundation^{31}</td>
<td>Measuring increases in life expectancy; Timeframe bounded metrics (&lt;18 mos, 18 mos, 18+ mos.)</td>
</tr>
</tbody>
</table>

Taking cues from industry with ROI (return on investment), performance metrics used to gauge partnership and project success varied amongst DFFs. The most common metric cited was an increase in life expectancy for an average patient (seen in bold in table above), with CFF, LLS, and PCF all measuring increases in life expectancy (or survival rates). This was felt to be a metric that would resonate with all constituencies including patients, and kept the focus firmly on results-oriented projects. Six DFFs used derivations of pipeline progress through the drug discovery and development value chain. ADDF rationalized the project progress by dividing by dollars invested, whereas both MJFF and CFF used an internally-developed point scoring system. One proxy of project (not pipeline) success was the amount of follow-on funding per dollar invested, which was captured directly by ADDF and MJFF, and indirectly by MRF. The level of detail capture varied as well. For example, the Multiple Myeloma Research Foundation drilled down into the number of days from final protocol to first enrolled patient, identified key opportunities to “keep the trains moving”, and shaved almost 40% of the original measured time. Nevertheless, few standardized performance measures that assist DFFs with resource allocation making decisions exist.^{41}
Discussion of Best Practices

Disease focused venture philanthropy (DFVP) is a relatively new business practice in the disease focused foundation industry. Often, details about best practices are omitted or glossed over from DFVP literature. This section discusses key DFVP practices observed at the level of the DFF. These processes are broken out into 4 categories: Risk Management, Partner Management, Value Drivers, and Organization. Interspersed throughout are questions that a DFF and/or potential DFVP partner would be advised to consider.

Risk Management

*Program vs. Project-Investing*

The risk exposure of the DFF can vary depending on whether they choose implement a purely program investing strategy, or fold in a few partner-based investments. Most of the DFFs with DFVP programs engage in a program investing strategy. A program-based process conducts due diligence at a drug candidate level. The focus is on a single project that will move the potential therapy one step closer to commercialization. The DFF reimburses only direct project costs. Expenses that are not directly attributable to drug development are not covered. The higher risk partner-based investing is utilized when the company has multiple programs or a platform technology with high potential clinical impact. The scope is broader because the diligence encompasses questions about the partner’s senior management, business model, other pipeline programs, and investors.

If program-based investing is like dating, then partner-based investing is like marriage. A key difference between traditional venture capital and DFVP is that VC’s always invest on a partner level, whereas DFVPs almost always prefer to invest on a project-basis. Each relationship comes with its own implicit relationship contract, or deal structure. Program-based DFFs universally stick to milestone-driven grants with a percentage of royalties and a cap on the original investment. This financial instrument is easy to comprehend with negotiated deliverables and milestones, and comes with an expiration date of 1 to 2 years.
A middle ground between milestone-based payments and equity investments are warrants and options. Warrants are a type of financial instrument that gives the holder, the DFF, the right to purchase a certain amount of stock (usually common) at a certain price (usually between its current value and future projected value) during a set duration of time. An option is similar to a warrant in that gives the holder the right to buy the partner’s common stock at a certain price before a certain expiration date. The substantive difference between a warrant and an option is that a warrant lifetime is much longer (e.g. 5 years) than that of an option (e.g. 6 months).

DFFs that engage in partner-based investing utilize a combination of equity, warrants, and options. Equity investment implies that the DFF is investing in the company and its employees, capital equipment, and intellectual property. This necessitates greater diligence from a capital risk standpoint. For most DFFs with limited foundation staff, most of this diligence is outsourced to external consultants. To underscore the difficulty of partner-based investing, only 3 of the 11 DFFs analyzed in the Data and Results section of this report augmented their portfolio with partner investments. These DFFs are Epilepsy Therapy Project, Juvenile Diabetes Research Foundation, and Leukemia and Lymphoma Society.

**Portfolio Diversification**

All the DFFs interviewed employed a diversified portfolio strategy that sought to maximize limited funds and resources. Portfolio diversification is one area that DFVP differs from traditional VC models. The partners of a venture capital firm usually create an investment thesis to guide their portfolio investing strategy. These theses act as broad guidelines as to what constitutes an attractive investment, and can specify any number of vectors (e.g. industry, team experience, stage of development, geography, etc.) DFFs, however, cannot truly create an investment thesis. There are no historical business models that can be emulated. No previous or peer investment funds or investments in the DFVP have published fund results allowing for comparisons between different DFVP models and outcomes.

Therefore, DFFs are left with embracing the “multiple shots on goal” approach, with its concomitant risk. If one layers in scientific and regulatory risk, it becomes clear that the DFF must be frank about the high potential for multiple failures before a success event. From a risk appetite perspective, if 9 out of 10 projects fail (not an uncommon event in life sciences investing), is that too much for your DFF to stomach? If so, then your DFF would need to focus
on “safer” bets. (“Safer” may be defined along the scientific and/or drug development value chain axis.) One perspective that a DFF like the Leukemia and Lymphoma Society used was to look at their development pipeline like a “medium-sized pharmaceutical company.”

The capital that the DFF provides in a partnership may be the highest risk capital at play. Several DFFs that focus on orphan diseases like the Cystic Fibrosis Foundation have deliberately decided to move into higher risk activities like distribution of clinical therapies to patients. They do so after examining the market failure in these areas and concluding that their risk capital is necessary.

According to Sohini Chowdbury, the Michael J. Fox Foundation for Parkinson’s Research has had to think long and hard about their risk appetite. It is all well and good to proclaim that your DFF invests in “high risk, high reward” projects. It is another thing altogether to report somber results back to your patients and donors.

In a hypothetical but very realistic case, let us say that a DFF funds 10 projects with commercial partners in the past 5 years. One project produces a candidate worthy of a clinical trial. Five show data that adds to the general body of knowledge of the disease, and the four remaining projects are dead ends. Is this an unacceptable outcome?

On the opposite end of the spectrum, let us say that another DFF also funds 10 projects in the past 5 years. This DFF deems all 10 projects to have “succeeded” by certain metrics (e.g. progression to next development milestone, increasing life expectancy, etc). Is this too safe? If no projects fail, then contrary to what the annual report and website states, your DFF may be playing in the “low risk, low reward” sandbox.

**Partner Management**

**Partner Sourcing**

For the purposes of this paper, partner has been construed as a for-profit entity, usually a biotechnology or pharmaceutical company, who is engaged in developing and selling therapies, tools, and services in the life sciences industry. A partner, writ large, is any person or
organization (external to the DFF) that engages in a relationship with the DFF designed to achieve mutually reinforcing goals for both parties.

Thus partner management will depend on the makeup of the counterparty. All DFFs analyzed in this study engaged in basic research grant funding. The partners in this NIH-style peer-reviewed, study section grant selection process are the academic investigators who lead labs in university and research hospital settings.

DFFs that fund outcome-based translational research in addition to basic science add another category of partners into the mix. Depending on the translational activity, these partners can be academic investigators, CROs, or biotech companies. A DFF who is looking to move into adding translational partners grapples with ensuring that their basic research funds produce promising science that can be moved into the next stage of the drug discovery value chain. The upfront diligence involves finding suitable potential partners who are comfortable and have experience with the disease or therapeutic area of focus, or are willing to invest the resources to gain appropriate expertise. CROs are uniquely suited to be partners for DFFs in the translational realm. The Cystic Fibrosis Foundation and other DFFs have worked aggressively to engage, educate, and outfit top CROs to cut down cycle-time. Other DFFs have created an informal, internally validated “short list” of CROs and other partners that it knows can quickly and capably execute pre-clinical and other validation activities.

Finally, DFFs who support clinical trial development deal with another set of commercial partners. Those who do not venture past Phase 1 and/or Phase 2a trials deal with either a CRO who specializes in safety clinical trials and/or a small, private, VC-backed biotech firm. It is rare that large, public pharmaceutical or biotech companies sponsor these early human trials, especially if the purported market is small or the science is still relatively unknown. It is only when the program has been properly “de-risked”(usually past Phase 2a, also known as “proof-of-concept” trials) that the larger players become interested.

The ideal partner for Phase 1 or Phase 2a trials is the smaller, private, biotech company. Your program would likely make up a larger portion of their portfolio than that of a large pharma, so there would be more attention paid to your project. The DFF monies provided would be non-dilutive capital, and would therefore be a welcome source of cash. There would be fewer
bureaucratic layers of management to deal with for the DFF. Big pharma is rarely interested, especially in orphan indications. Furthermore, their hurdle rate is even higher, and they are prone to be extremely risk-averse due to loss aversion.

There is anecdotal data to suggest that big (and small) pharma and biotech may be coming around to orphan indications and niche markets as lucrative sources of future income. Successful public biotechs like Genzyme and Shire have large market capitalizations based on rare disease franchises, and others are following suit. Venture capital investments into rare disease drug development are not unheard of. Third Rock Ventures, a Boston based venture capital firm, has sought opportunities into rare genetic diseases like X-linked hypohidrotic ectodermal dysplasia and adrenoleukodystrophy, both orphan diseases with less than 200,000 patients in the US.5 For orphan diseases, however, the small “hand-to-mouth” VC-backed companies were thought to be “hungrier” to work with DFFs.

DFFs who engaged in late stage clinical trials viewed large pharma as carriers of the touch for the larger Phase 2b and Phase 3 studies. There was a general understanding that large, public life science companies viewed a project to be properly “de-risked” if it successfully met all its primary endpoints for Phase 2 proof of concept trials. Again, folding in a large company as a partner was understood to add additional complexity to the DFF’s partner management strategy.

All interviewed DFFs articulated that the drug development activities bookended by target ID and Phase I trials was the “sweet spot”. This “valley of death” was clearly where most DFFs felt that DFVP could address market failure through their risk capital. Additionally, DFFs who were most forward-thinking began to research potential partners well before any projects were on the horizon. They looked closely at the level of experience and background of the companies, whether they possessed the appropriate scientific and clinical expertise, and the amount of effort the DFF would need to employ to educate them on their disease, endpoints, clinical care methodology, etc.

**Project Management, Governance, and Expectations**

Once the DFF took on a partner, DFVP program managers emphasized that setting clear upfront expectations was key to a good working relationship. For almost every for-profit partner, this
would be their first time working with a DFF. Part of the DFF’s upfront engagement entailed educating their partners on how DFVP was executed in their particular DFF. Defining and clarifying roles and expectations from both parties set a professional tone moving forward.\textsuperscript{16}

In addition to roles explication, many DFFs followed a continuous improvement philosophy through their annual evaluations. They took frank looks at the relationship and the interactions between the DFF and the partner.\textsuperscript{16} DFFs sought to understand if their partnerships were fruitful through partner performance metrics.

Project oversight was usually managed by a cross-functional team comprised of foundation staff, company management, and project managers. Frequency, as seen in the Results and Analysis section, varied from quarterly conference calls to annual meetings. Most DFFs checked in at least twice a year to ensure that critical path items were on track on the partner’s workplan. Outside of these formal interactions, there were multiple casual touchpoints where the DFF assisted with connecting the DFF to the right scientific experts, helping to find a good CRO with experience in this particular patient population, or even going so far as actively helping the company to fundraise during their next round of financing.

The sentiment was often expressed that if a project consumed a substantial amount of a DFF’s funds, and was rather risky from a scientific or clinical standpoint, it required heavy DFF oversight. The heavy-touch approach was surprising because best practices literature would suggest that a risky project with many untested assumptions needed the opposite. A light-touch governance structure would allow quick decision-making autonomy to adapt to shifting information and new information. A governance structure that insisted on weekly phone calls with detailed updates might smother a large risky project with too many cooks in the kitchen. Balancing accountability with the correct oversight flexibility would enable project success to explore high-risk, high reward areas. A key recommendation would to ensure project management that is consistent with the riskiness of the project.

\textbf{Next Steps and Forward Thinking}

Another issue that many DFFs face when they first enter into DFVP partnerships is that of clear next steps. It is essential to detail explicit next steps that would be taken if the project is successful. Corresponding resources should also be outlined and quantified if possible. Who is
going to execute the next step? How far is your DFF willing to go to develop the therapy? Human trials? Phase 2? Does your DFF know exactly how much you have to “de-risk” the program for it to be attractive enough for another partner to step in? If the program is successful, is the commercial partner’s investors and management committed to developing it to the next clinically relevant milestone?

The Myelin Repair Foundation grappled with this issue as they learned how to better de-risk programs for potential downstream partners. This involved going beyond target identification and into target validation, as well as cost avoidance. For Rusty Bromley, this encompassed educating themselves on internal MS programs in partners’ pipelines, and understanding how MRF-funded projects stacked up against these internal programs.

The Epilepsy Therapy Project tackles next steps by explicitly requesting information about commercial implications of the project, and its licensability. It asks questions that seek to connect the proposed project with progress towards a cure by probing into its commercialization strategy.41

**Value Drivers**

Every DFF claimed that they brought non-cash value-added assistance to DFVP partnerships. Their financial proposition as non-dilutive capital notwithstanding, their value proposition fell in five main buckets: 1. Clinical networks, 2. Supporting a cast of characters, 3. Access to the best science, 4. Good Housekeeping seal of approval, and 5. Knowledge management/collaboration. All these resources involved pro-active engagement with external partners and suppliers. Most DFFs with DFVP programs engaged in at least one of these services.

**Clinical Network**

For DFFs anticipating clinical trial testing, an integrated, clinical network with instant access to the relevant patient population could speed recruitment and reduce redundant paperwork. The Multiple Myeloma Research Consortium (MMRC) was created by the Multiple Myeloma Research Foundation (MMRF) as a legally separate organization to pull together supporting infrastructure to expedite clinical trials. The MMRC now consists of 13 academic centers and a multi-institutional tissue bank with 1300 tissue samples and 2100 matched blood samples
representing 1800 patients. For the MMRF, this was key to reducing “mundane inefficiencies” associated with clinical trial conduct (e.g. budget, IP, publication, disclosure, clinical milestones) with standardized clinical trial agreements. The Foundation Fighting Blindness (FFB) also created the National Neurovision Research Institute (NNRI) to support translational research by pooling resources to aid validation and clinical activities.

Accelerated Cure Project also recognized the need for a large-scale biorepository, and created the MS Repository to collect samples from MS patients. ACP is accessible to investigators in exchange for data created using these samples. The Cystic Fibrosis Foundation also created a clinical trial network known as the Clinical Trials Network within the Therapeutic Development Network, which acts for all intensive purposes like a CRO that can plan and run a clinical trial from soup to nuts. The Christopher & Dana Reeve Foundation, a DFF that is slowly easing into DFVP, established the North American Clinical Trial Networks (NACTN). In fact, NACTN was instigated by neurosurgeons who pushed for a robust clinical network focused on spinal cord injuries.

Tied closely to clinical consortiums are comprehensive patient registries. This is an especially key value drive for DFFs focused on orphan or homogenous small-market diseases. The time and associated cost of patient recruitment can drag on for years and terminate trials if patients cannot be expediently enrolled. The Cystic Fibrosis Foundation found that maintaining a current, comprehensive patient registry with clinical and demographic data helped to inform partners about disease characteristics as well as to reduce clinical trial durations. Another DFF, Muscular Dystrophy Association, observing the lessons of Genzyme’s Myozyme program for Pompeii’s disease, found that access to patients was a critical rate-limiting step that slowed clinical trials and drove up costs. Thus they worked with patient advocacy group to help create a comprehensive patient registry.

**Supporting a Cast of Characters**

Biotechs who partner with DFFs use CROs, labs, animal testing facilities, and other auxiliary services to complete their projects. DFFs accelerated project execution by pro-actively creating centers of excellence for supporting services. The services ranged from site initiation to clinical-grade drug manufacturing, and depended on the stage of the DFF-funded projects. DFFs also
educated these side players, bringing them up to speed and financing their build-outs if necessary.40

As mentioned in the previous “Partner Sourcing” section, the Cystic Fibrosis Foundation found that creating a short list of approved qualified vendors, CROs, clinical sites, development experts, and other service providers expedited pre-clinical and clinical project execution. Foundation Fighting Blindness’s Preclinical Assessment Centers created Preclinical Assessment Centers to expedite preclinical validation for companies researching potential clinical indications.41 The Christopher & Dana Reeve Foundation created a central animal lab that served academic labs, and intend on expanding these services to future commercial partners.

Access to the Best Science

Because all DFFs continued their relationship with the world’s leading academic experts in their fields, these same scientific advisors became a valuable resource for commercial partners. The advice they provided ranged from scientific clarification to helping to design and evaluate clinical trial data. Many DFFs, including Cystic Fibrosis Foundation, felt that many potential partners sought them out because they had unfettered access to top scientists. Their intellectual capital, often provided free of charge, also frequently led to further side collaborations and was one of the most commonly cited non-cash value-added assistance provided by DFF to their partners.

Good Housekeeping Seal of Approval

The phrase “good housekeeping seal of approval” was repeatedly uttered by almost every DFF interviewee.40 As DFFs have limited cash to distribute, it became increasingly obvious that leveraging their investment to attract additional capital for partners was essential. Whenever a DFF established a partnership, their PR department would ensure that a press release was sent out to announce the partnership. In addition, any follow-on funding, license agreement, or acquisition would trigger another press release.21

The intended audience for these announcements was often potential partners, licensors, or acquirers. By bestowing their blessing upon a particular project, the DFF conferred a “foundation halo”. Wise DFFs and partners managed the signaling aspect of the relationship closely to ensure that potential investors remained updated and interested. The Accelerate
Brain Cancer Cure (ABC2) foundation, for example, traveled alongside one of their commercial partners to actively assist in raising their $30M 2nd financing round.

**Knowledge Management and Collaboration**

Knowledge management and collaboration was a DFF value driver developed by frustrated DFFs who did not understand why their academic investigator grantees were reluctant to share data and results. DFFs now deliberately build-in collaboration and information sharing amongst all stakeholders in their contracts. As mentioned in the previous Partner Management section, this sets clear expectations for the commercial partner as to how the information will be disseminated. For example, Myelin Repair Foundation and Prostate Cancer Foundation explicitly state in their contracts that all results, positive or negative, will be shared with the DFF and published within the year. This is a necessary pre-condition of the relationship and is not negotiable.

DFVP officers acknowledged that the knowledge sharing amongst commercial partners did not occur organically due to concerns about IP and trade secrets. Indeed, DFFs signed confidentiality provisions with each company, so the DFF would often act as the central hub for sharing observations to respect the Chinese wall between multiple commercial partners.
Another effective medium for multi-stakeholder collaboration was through conferences, roundtables, and neutral forums. By convening under the banner of the DFF, the DFF can provide air cover for academics, regulatory agencies, clinicians, and companies to interact in real-time and share information. To paraphrase Russ Bromley of the Myelin Repair Foundation, “Cajoling and convincing vs. command and control is how we encourage knowledge sharing”.

Additionally, the MRF and JDRF expressly encouraged projects that address complex problems that can only be addressed with interdisciplinary and multi-institutional efforts. Encouraging team-based science\textsuperscript{41,42} has the side benefit of educating up and coming primary investigators in the challenges of drug development.\textsuperscript{24} Early engagement of upstream drug discovery partners can help the DFF to articulate how funding a basic research project may lead to a realized therapy.

\textit{Value Drivers dependent on Partner Engagement}
The value drivers that your DFF develops will depend on the intensity of partner engagement and education. The DFF acts a central knowledge hub; collection, vetting, disseminating validated data and updates. It acts like an orchestra conductor who is not making music per se, but guides different sections to harmoniously play from one music score. DFFs who provide these non-cash value additions attracts competent partners who are eager for access to the most current scientific thinking and projects in their disease space.

From a regulatory standpoint, DFFs like the JDRF will engage and advocate on behalf of their commercial partners at the FDA, which is essential for more obscure, orphan diseases, regarding relevant endpoints. It can go so far as to propose new, more relevant clinical endpoints for trials. CROs and labs who want to establish lab expertise can look to the DFF for assistance. It is the DFF’s prerogative to be honest and unbiased, thereby inducing collaboration between partners as a trusted intermediary. DFFs that pursue formal advocacy efforts at the FDA and physician groups are careful not to align themselves with any particular commercial partner to avoid potential conflicts of interest. The efforts of DFFs to educate foundation staff and volunteer constituencies, as internal partners, about the drug discovery and development process and risks should also be lauded.

**Organization**

Like the business world, the DFVP business model that any one DFF embraces is unique. There are as many DFVP models as there are DFFs. Much of how your DFF envisions DFVP will depend on organization-specific characteristics. These include where the funds come from, story of origin, patient advocacy, where the science is, who runs the DFVP programs, and who you consider to be your stakeholders.

**Sources & Uses of Funds**

The sources of cash will affect how your DFF transacts DFVP partnerships. The makeup of your DFF, whether it is a family foundation with a concentrated donor pool, or a large foundation supplemented with government money and grants, will help dictate the expectations, wishes, and goals of the DFVP programs. What is your donor makeup? Are they educated philanthropists?
This will also dictate the level of detail and frequency of updates. What is the level and type of information your donors are demanding? The 2008 and 2009 annual reports of many DFFs contain audited financial statements without program level granularity. This is like a public pharmaceutical company choosing to disclose how much was spent on R&D at a company level, but not on a therapeutic level.

The Lymphoma and Leukemia’s Society 2009 Annual Report contains a good example of a concise statement that is relatable to patients and donors. Its Consolidated Statement of Functional Expenses breaks down in detail where the money was used down to awards, grants, travel, etc. The Alzheimer’s Drug Discovery Foundation’s 2008 pipeline report is another example of how a DFF can examine, analyze, and publish project-specific data.

One question DFFs might ask themselves is whether placing DFVP centrally is attractive to donors. For example, the Myelin Repair Foundation had found that DFVP attracts a certain class of donors that might have never given to the MS Society, but are interested in MRF’s business model. For a foundation like the Michael J. Fox Foundation for Parkinson’s Research, DFVP resonates as they have chosen not to have an endowment. Thus, the amount they are able to distribute is intimately tied to how much they can fundraise from new and existing donors.

In addition, DFF sometimes separate the pool of monies allocated for basic research programs from that of translational research. Others use one pot from which all projects are funded. Still others, like the CFF, have “unspecified” pools that fund new, out-of-cycle funding. MRF has a separate pool for small pilot projects ($25-30k/yr) for 1 year. If these pilots pan out, then they are fleshed out into more substantive, comprehensive project proposals. There are as many ways to slice the aggregate pool as there are DFFs, and each DFF has a different tack of balancing flexibility with predictability.

**Story of Origin**

The operation of your DFVP model depends on your story of origin. Is your DFF a stand-alone or wholly-owned subsidiary of a parent organization? The DFVP programs that the MS Society runs will look different from that of the Myelin Repair Foundation. The MS Society has legacy expectations with diverse products and programs, including catering to patient groups. A de
novo DFF like the Myelin Repair Foundation does not have legacy grant-making processes and its accompanying expectations.

DFFs looking to create DFVP subsidiaries must carefully navigate the culture clash between the parent and subsidiary, especially if donors want to reallocate their funds from the parent organization to the new subsidiary. A parent foundation, like the Muscular Dystrophy Association (MDA), might choose to launch a separate DFVP fundraising entity like the MDA Venture Philanthropy arm. MDA maintains a legal and cultural firewall between itself & MDA Venture Philanthropy to deliberately cultivate a different, more risk-embracing culture at MDA Venture Philanthropy.

**Where is the Science At?**

The current level of scientific understanding of your disease will affect grant allocation in the drug development process. If the underlying biology of the disease pathologies and progression remains unclear and uncertain, with few or ineffective tools, then the primary focus of the DFF will logically remain at basic scientific stage, with few forays into translational activities. The DFF usually works with the NIH at this point to try to bring more attention and dollars to their particular cause, and strategically allocates DFF funds to complement NIH funds. Because the scientific risk is highest at this point, deciding which projects to move forward into target validation can be a moving target.
Figure 5: DFVP Approach Mapped on Science/Medicine Question vs. Complexity of Solution

A 2x2 matrix can help delineate the main thrust of any DFF program. On the x-axis, is your DFF tackling a science or medicine question? That is, is your DFF trying to figure out what the question is, or do you have a pretty decent grasp on the question so you’re likely to come up with viable solutions? The y-axis addresses the complexity of the potential solutions. Solution complexity, of course, is part and parcel of problem definition. If the problem is relatively straightforward, the DFF can be relentlessly focused on a few potential therapies.

If the problem is multi-factorial, or if the disease focus spans multiple pathologies and etiologies, then a more a diversified approach is called for. This requires the foundation to be brutally frank about the current scientific state of affairs. Self-review should be performed yearly to ensure correct triangulation of where the DFF can be most effective in its grant allocation process. This can be clearly reflected in the DFF’s mission statement. Are you looking for a cure? A disease-modifying therapy? These are two related but different goals. Are the questions you are seeking to clarify ones that the DFF can help answer? Is it the problem a well-defined one, and is there a clear action plan? Are you aiming for a cure or a care? Is this a moving target?

Scientific risk was felt to be the most unpredictable and unmanageable risk in disease philanthropy. Variations on “science is a random walk, hard, and messy” echoed from every
DFVP officer interviewed. Mitigating this risk was felt to be amongst the most challenging issues that a DFVP program faced.

As Russ Bromley of the Myelin Repair Foundation said, “we focus on tractable problems and workable solutions.” The MRF broke down its mission statement into discrete, quantifiable goals with “expiration dates” that held itself publically accountable. For example, they had set forth a target of identifying myelin repair drug targets by the end of 2009, and getting the 1st drug into Phase I trials by 2014.41 FasterCures also identified that well-defined problems with a clear path to an attainable goal(s) was essential for successful collaborations.41

Patients

There were varying levels of patient involvement in the DFFs surveyed. Few had little to no direct patient interaction. Others had patient representation at a board or review committee level. For all levels of patient engagement, managing patient expectations was key. The balance between driving excitement and dollars towards funding projects and remaining dispassionate as a neutral clearinghouse was one that each DFF dealt with in its own way. If patients were part of the DFVP decision-making process, it was felt that they provided best input regarding potential clinical impact. One such program was the Faster Cure’s Patients Helping Doctors (PHD) initiative that sought to empower “patients to be part of the research enterprise”.

HR

DFFs that sought to utilize DFVP to diversify beyond their traditional grant-making models also found themselves managing tensions within their internal organization. Whether applying DFVP narrowly or on a foundation level, many of the common problems that cropped up are listed below.

- Control/territorial issues between foundation staff and donors – who has decision-making authority
- Culture clash between business world and non-profit world, suspicion, mistrust
- Lack of financial savvy to conduct due diligence and transact deals
- Divide between the employees who are sourcing deals and the rest of organization
- Financial resources at disposal (short-term and long-term)
• Perception of cannibalizing fundraising monies from parent organization
• Grant allocation between basic research, translational research, and clinical studies
• Different risk appetites
• Effect of recency bias, recent financial collapse of fall 2008 and public flogging of financial institutions & corporate greed. Touted “business” principles tainted by financial debacle. High anti-corporate sentiment among public.¹⁹

Historically, DFF staffs were career non-profit employees who had PhD’s with relevant scientific expertise. The old paradigm was one of a black box, where donations were taken in as inputs and grants were distributed as outputs. The new, current paradigm demands foundation staff with financial acumen in addition to scientific research experience. The new generation of philanthropists wants more control and transparency into resource allocation decisions. DFVP directors must mirror this attitude. Most of these new donors have created wealth through hands-on entrepreneurial ventures, and fervently subscribe to infusing and transplanting successful business practices into the DFF world. Those who give generously often expect a measure of input, such as sitting in on business advisory discussions of potential partners. Other donors who are frustrated with the slow progress of disease research agitate to bring lean improvement projects to DFF-funded programs.

The backgrounds of the staff running the DFVP programs were a mix of academia and industry. The best “blend” came from scientists who had done research in that particular therapeutic area, moved into industry to run R&D, then ran Business Development functions at both small and large life science companies. Much of setting up a successful DFVP program required knowledge of how commercial partners made money and understanding their capital and incentive structures. Thus, the relative industry savvy of these directors shaped how the DFVP programs planned for failures and assessed risk. Furthermore, the business acumen of these DFVP directors dictated the sophistication of financial instruments of a potential deal. Most of the due diligence was outsourced with guidance from the DFF, and a DFVP director with business experience would know hot button issues for further assessment.

**Stakeholder Analysis**
A final self-reflection exercise might be one of stakeholder analysis. List all parties that might have an interest in your DFF. These could include small donors, large donors, volunteers, foundation staff, foundation board, academic scientists, clinician-scientists, clinicians, patients, patient’s families, biotech companies, large pharma, regulatory agencies, CROs, etc.

Next, try to clarify who is your primary customer? That is, who are you trying to please above everyone else? Then, identify your partners, consultants, and suppliers. Partners are entities that you need to help serve your customers. Consultants are entities that provide services and perform non-core functions, and your suppliers provide key inputs. Finally, who are your shareholders? Who has a vested interest in making sure your DFF achieves its goals? Who has the most to gain?

**Answering the Venture Philanthropy Skeptics**

Venture philanthropy has always has its healthy share of skeptics. They claim that venture philanthropy is another trendy term coined by buzzword-happy consultants. At its worst, venture philanthropy has been accused of painting a pro-business veneer on the organization. Critics have decried giving “non-profit organization(s) an extreme commercial makeover”, often to the detriment of foundation staff. However, it is wise to put the impact of DFVP in perspective. The government is still the largest “foundation” that distributes funds. Its resources dwarf that of DFFs. The lay public continues to expect that the government will allocate resources to maximize public welfare.

It is clear that there is no magic formula of entrepreneurial practices linked to social outcomes for DFFs who are thoughtfully engaged in DFVP. The DFF community is mostly aligned with DFVP, and whether one calls it “venture philanthropy”, “strategic grant-making”, or “measurable giving”, the kernel of venture philanthropy has existed for decades. The difficulties that DFFs face is in the execution, and embracing change management that goes far beyond appointing a Vice-President of Venture Philanthropy.

Moreover, there is sense of urgency that DFFs can communicate through their DFVP efforts to their stakeholders. Donors, many of whom are savvy technology users, want to see tangible results from their contributions and sophisticated use of technology. For many of these diseases, there is a clear unmet clinical need and patients are dying. Clinicians are frustrated
with their lack of therapeutic options. Academic scientists are excited to see their research translated and are rapidly learning about commercialization challenges. Foundation staff are looking to business thought leaders and DFFs that have paved the way. Boards of directors have read about venture philanthropy and social entrepreneurship and are eager to adopt innovation, or at least give the perception of doing so. Large pharmaceuticals wait to see if DFVP can de-risk programs enough for them to want to invest, license, or partner. Regulatory agencies receive continuing education from DFFs as to the latest science advances. VC-backed life science companies need money for the unsexy translational activities and pre-clinical validation.

**Final Thoughts**

In the past, scientific advances that have led to blockbuster therapies were thought to be “low-hanging” fruit, as single-cause diseases were tackled with relatively straightforward small molecule solutions. Multi-factorial diseases with environmental, epigenetic, and genetic factors like most cancers and immunological pathologies are currently forefront in R&D pipelines today. As their level of complexity increases, the required level of collaboration between different academic and scientific disciplines increases as well. This neatly explains how disease focused foundations as “neutral open forums” are pivotal in cogently expanding the body of knowledge and moving therapy development forward in an interdisciplinary way.

To paraphrase Dr. Simons of PCF, the key value driver for DFFs is the “sense and authenticity of urgency” that DFFs can communicate from their “bully pulpit”. Dr. Louis DeGennaro from LLS echoed Dr. Simon’s sentiments that LLS was well-placed to inject sense of “urgency to the situation”, and could crisply crystallize the frustrations that donors and patients feel with the lack of available disease-modifying therapies as a function of DFF funding.

Disease focused foundations occupy a rare and privileged “trusted place for progress in society”. There are few organizations in society that the lay public implicitly trusts. Thus, fundamental to a DFF identity is that of an “honest mediator” that “transparently” wields the “power to convene” to solve market failures in the drug development process. A DFF has extremely limited resources relative to its for-profit counterparts. But if your foundation sets itself up as the neutral “exchange of scientific and medical knowledge”, it may have more power to fund bring
crucial therapies to market by funding transformative, translational research with clinical relevance than any other institution today. 42

Further Questions to Explore

Are there therapeutic areas that lend itself more to DFVP investments? Orphan diseases, any disease with a captive patient population, high mortality rates with few clinically effective therapies may fall into this category. Additionally, any aging or neurodegenerative disease that disproportionally affects baby boomers might be ideal, as high-net worth donors are most likely to be affected with these diseases. Others identified include reproductive and international health. 9 The flip side of this question is: Are there foundations that should not enter the DFVP space? For example, the American Cancer Society had proposed an in-house venture philanthropy arm, but decided for unclear reasons to pull back. Not all DFFs may be suited to strategically de-risking pre-clinical assets with commercial partners.

Another area of future research is the dearth of highly functional markets and capital flow in biomedical disease research. 41 This creates inefficiencies, information asymmetries, and high transaction costs for both the DFF and their potential partners.

A related line of inquiry would be a proposal for a standardized informed report card for DFFs. If one thinks about public companies, and the metrics that are most commonly used such as earnings per share, net income, return on assets, etc, a philanthropist seeking to make donations needs comparable data on returns across DFFs so as to better identify top performing organizations. For this to occur, trend data from all DFFs would need to be made public. This data would need to be distilled into 4-6 key DFF/DFVP metrics to determine the overall growth and trajectory of the DFF. These could be shared with the Board of Directors and key donors. They should be useful and concise enough that all stakeholders could recite them from memory. Controls would need to be identified to test the fundamental assertion that DFVP accelerates development of a cure.
Appendix A– Brief Overview of DFFs

1) Alzheimer’s Drug Discovery Foundation (ADDF) / Institute for Aging\textsuperscript{21,25}
   a) ADDF’s hybrid investment vehicle called Fund for Alzheimer’s Drug Discovery\textsuperscript{21}
   b) In 2008, 9 of the 70 AD drug programs in current clinical trials received some support from ADDF
   c) Between 1998 to 2006, total of $28M was disbursed; 137 academic and 19 industry projects for 116 unique PI’s: 112 drug discovery (69%), 21 clinical stage (16% of funds), 15 early detection (biomarkers, testing, imaging), 8 preventing/risk reduction.
   d) From 1998 to 2006, $22M invested in 94 drug discovery research programs in 12 countries, 38 (40%) advanced forward at least 2 key milestones in drug development process, 13 advanced 1 stage
      i) Drug development stages defined chronologically as: target discovery, target validation, lead discovery, lead validation, lead optimization, proof-of-concept, pre-clinical development, clinical trials. Proof-of-concept studies represented 30% of portfolio
      ii) Categories: Neuroprotection, animal models, anti-amyloid, anti-inflammatory, antioxidants, anti-tangles, cognitive enhancers
      iii) Smallest grant: $25k
      iv) Largest grant: $1.15M
   e) Performance metrics for success:
      i) Ratio of scientific progress as measured by movement through stages through drug discovery and development divide by dollar invested. Higher numbers indicate more progress per dollar spent or better project selection
      ii) IP creation: 50 (56%) new IP secured from 94 programs, 16 (17%) of these have been licensed

2) Christopher & Dana Reeve Foundation\textsuperscript{39}
   a) Four different funding mechanisms
      i) Investigator initiated individual grants (focus on rehabilitation therapies as sub category)
      ii) International Research Consortium (8 labs globally collaborating)
         (1) Core Labs (animal lab that is run by investigators in the fellows program)
      iii) North American Clinical Trial Networks (NACTN)
         (1) Started 6 years ago
         (2) Fully funded by DoD (Walter Reed Hospital)
      iv) Neuro Recovery Network (NRN) – activity-based rehabilitation

3) Cystic Fibrosis Foundation\textsuperscript{15,30,36}
   a) Therapeutics Development Program established in 1998
   b) Cystic Fibrosis Foundation Therapeutics (CFFT) established in 2000 as non-profit drug discovery and affiliate of CFF
   c) Can invest up to $25M (total) in DFVP efforts
   d) 8 areas of focus & research w/ 25 commercial partners
      i) Gene therapy: Copernicus Therapeutics
      ii) CFTR modulation: Vertex Pharmaceuticals, PTC Therapeutics
      iii) Restore airway surface liquid: Inspire Pharma, Pharmaxis, Sucampo Pharmaceuticals, Lantibio, Gilead Sciences
iv) Mucus alteration: Genentech
v) Anti-inflammatory: BioAdvantex, GlaxoSmithKline
vi) Anti-infective: Novartis Pharmaceuticals, Pfizer, Gilead Sciences, Transave, Kalobios Pharmaceuticals, Mpex Pharmaceuticals, Bayer Schering Pharma
vii) Transplantation: APT Pharmaceuticals
ix) 2 workout situations in past year: e.g. Altus Pharmaceuticals (case of cash-strapped biotech that discontinued program), CFF had to come in to take the IP, and sub-license Trizytek™ to Alnara Pharma

4) Epilepsy Therapy Project
a) 2 grant programs: New Therapy Grants Program, Commercialization Grants
b) 33 grants to scientists & entrepreneurs to move toward commercialization of lab concepts
c) 1 matching grant to increase interest in licensing a potentially safer version of an existing treatment
d) 3 seed-stage investments to support start-up companies
i) Nov 2009, partnership with NeuroTherapeutics Pharma (investment)
ii) Dec 2008, partnership with IntelliVision Technologies, Corp (grant)
iii) Dec 2007, partnership with Neuromed Pharmaceuticals (grant)
iv) Dec 2007, partnership with Neurologix, Inc. (grant)
v) May 2006, partnership with Unv of Wisconsin and NeuroGenomX (equity investment)
vi) April 2005, partnership with VistaGen Therapeutics, Inc. (investment)
vii) April 2004, partnership with Marinus Pharmaceuticals, Inc. (investment)
viii) March 2004, partnership with NeuroMolecular Pharmaceuticals, Inc. (investment)

5) Foundation Fighting Blindness
a) 2 grant programs: New Therapy Grants Program, Commercialization Grants
b) National NeuroVision Research Institute (NNRI) - relatively new division of FFB
i) Clinical arm of FFB
ii) Four areas:
   (1) Genetic Therapy
   (2) Nutritional Pipeline
   (3) Neuroprotective
   (4) Cellular Therapy

6) Juvenile Diabetes Research Foundation (JDRF)
a) JDRF Industry Discovery & Development Partnerships (IDDP) Program
b) IDDP Therapeutic Pipeline - 20 programs with 20 partners
c) 33 deals to date, only 1 equity-based deal with TolerX (3.5M of a 34M financing round on same deal terms as VC’s and other institutional investors)
d) $1.4B to date, started IDDP 5-6 years ago

7) The Leukemia & Lymphoma Society
a) 60 year history (longest amongst DFFs profiled)
b) Therapy Acceleration Program (TAP) launched in 2008 – Partnering w/ biotech companies – Split into 3 prongs
   i) Academic Concierge Division – Liaison between academic researchers and CROs for pre-clinical validation in preparation for FDA clinical trial application (60 projects as of Apr. 2010)
ii) Biotechnology Accelerator Division – Partners with biotech and pharmaceutical companies on gaining clinical efficacy

iii) Clinical Trial Division – Coordinates with cancer trial centers and patient registries to increase patient enrollment for Phase I and II trials

c) Biotech partners include: Aegera (Phase I/II), Memgen (Phase Ib), Celator Pharmaceuticals (Phase IIb),

8) Michael J. Fox Foundation for Parkinson’s Research37

a) Founded in 2000; $175M+ over past 10 years
b) Highest private funder in Parkinson’s disease research space
c) Business model = no endowment
   i) Therapeutic Development Initiative (TDI) ~$5M/year (industry-exclusive) for pre-clinical PD research
   ii) Rapid Response Innovation Awards – high-risk, high-reward projects with little to no existing preliminary data, but potential to significantly impact our understanding or treatment of PD
   iii) Target Validation Awards - PD-relevant pre-clinical model development
   iv) Clinical Intervention Awards - clinical testing of promising PD therapies

d) LEAPS (Linked Efforts to Accelerate Parkinson’s Solutions)41
   i) Proof of Concept to Phase I clinical trials
   ii) Multi-million dollar, multi-year grants w/ industry and academic components

9) Multiple Myeloma Research Foundation32

a) $13.8M in research program grants in 2008, $14.2M in 2007
b) $115M raised for multiple myeloma R&D development since inception
c) $14M invested in research programs since inception
d) MMRF Fund – Pre-clinical validation
e) Biotech Investment Awards – Expand validation and early clinical trials
   i) Aileron Therapeutics in 2008
   ii) Astex Therapeutics in 2008

f) Multiple Myeloma Research Consortium – Human clinical trials

10) Myelin Repair Foundation24

a) Accelerated Research Collaboration (ARC) “outcome-driven model”24
b) Founded 2003/2004
c) Projected $80M grant budget between 2010-2015 (3x as previous 3 yrs)
d) 40 projects funded between 2003-2010, 18 patentable inventions, 24 research tools, 19 myelin repair targets identified
e) Based on open-source, early stage academic collaboration: project design engages multiple labs; outcome-driven research projects; “Acceleration through Collaboration”
   i) IP framework: MRF files for patents, university that generated the idea keeps the IP, MRF markets IP to potential industry partners24
   ii) Currently 25-30 investigator-initiated projects, each project has 12-month deliverables, 2nd year funding predicated on hitting milestones

f) Approached 40 potential biopharma partners, 6 identified as good. Most industry not as well versed in myelin repair and validation.

11) Prostate Cancer Foundation31

a) $28M committed towards new research projects in 2008
b) Multiple grant programs:
   i) PCF Creativity Awards: $50-100k to investigators, 1 yr w/ option for follow-on funding
ii) PCF Challenge Awards: $300k-$1M/yr to at least 3 investigators on 3 year project
References
