Analytics for Financing Drug Development

by

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Submitted to the Sloan School of Management
in partial fulfillment of the requirements for the degree of

Doctor of Philosophy in Operations Research

at the

MASSACHUSETTS INSTITUTE OF TECHNOLOGY

June 2015

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Abstract

Financing drug development has a particular set of challenges including long development times, high chance of failure, significant market valuation uncertainty, and high costs of development. The earliest stages of translational research pose the greatest risks, which have been termed the “valley of death” as a result of a lack of funding. This thesis focuses on an exploration of financial engineering techniques aimed at addressing these concerns. Despite the recent financial crisis, many suggest that securitization is an appropriate tool for financing such large social challenges. Although securitization has been demonstrated effectively at later stages of drug development for drug royalties of approved drugs, it has yet to be utilized at earlier stages.

This thesis starts by extending the model of drug development proposed by Fernandez et al. (2012). These extensions significantly influence the resulting performance and optimal securitization structures. Budget-constrained venture firms targeting high financial returns are incentivized to fund only the best projects, thereby potentially stranding less-attractive projects. Instead, such projects have the potential to be combined in larger portfolios through techniques such as securitization which reduce the cost of capital.

In addition to modeling extensions, we provide examples of a model calibrated to orphan drugs, which we argue are particularly suited to financial engineering techniques. Using this model, we highlight the impact of our extensions on financial performance and compare with previously published results. We then illustrate the impact of incorporating a credit enhancement or guarantee, which allows for added flexibility of the capital structure and therefore greater access to lower costing capital. As an alternative to securitization, we provide some examples of a structured equity approach, which may allow for increased access to or efficiency of capital by matching investor objectives. Finally, we provide examples of optimizing the Sortino ratio through constrained Bayesian optimization.

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Acknowledgments

I gratefully acknowledge my advisor Andrew Lo for his guidance throughout my research, and for starting my involvement with financing for drug development which has been a particularly rewarding subject that I have enjoyed contributing to. Thank you for encouraging me the work on problems that interest me, and for your passion for the future of biomedical funding and clinical research.

In addition, I acknowledge Roger Stein, for serving in a co-advisor capacity throughout my research, for his persistence in pushing me to work hard, for his extensive comments during my thesis preparation, and for his friendship. Thank you for actively checking in on my progress, for involving me in your research, and for valuing my input. Your communication and guidance have been invaluable to me.

I would also like to thank my collaborators, Jose-Maria Fernandez for his detailed analysis in preparation of the original megafund work and for his friendship; Austin-Gromatzky for his extensive literature review for our orphan work and assistance in developing assumptions for parameters; Nora Yang for her many hours of data collection and discussions on parameter assumptions for the NCATS work; John McKew for his keen insights and constructive feedback on the NCATS work; Adlar Kim for his insights for extending the MATLAB software in practical directions; and the many panel discussants at conferences organized by Andrew Lo who are too many to name. I also thank my thesis committee: John Guttag and Dimitris Bertsimas who have encouraged me to see the big picture.

My friends and colleagues in the MIT Operations Research Center have made Boston an amazing experience, and have served as a support system through difficult periods in my personal life. Finally I am grateful to my wife Rhea, and my family for their endless support and encouragement, without which I would not have finished this thesis.
In memory of my brother Ryan.
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Chapter 1

Introduction

Over the past 60 years, pharmaceutical research productivity has declined by approximately half roughly every 9 years as measured by the number of drugs approved by the Food and Drug Association (FDA) per billion US dollars spent. [80]. The financial performance in the industry has also waned, resulting in a loss of roughly $850 billion in shareholder capital among the top 15 companies in the industry from December 2000 to February 2008[30]. Another hurdle faced by the industry is the patent cliff caused by the expiration of existing patents resulting in an estimated $113 billion of sales being lost to generic substitution between 2010-2014[73]. Regulatory hurdles are also increasing, with the growth of FDA regulations by word count increasing at about 12,000 words per year according to data analyzed by Regulatory Focus [26]. The budget for the NIH has also declined over the past decade, reaching an all time low (GDP adjusted) in 2013 as illustrated in Figure 1-1.

Numerous recent works address the economics of drug development, including estimates of historical success rates of clinical projects[17, 73, 36], clinical/research costs[73], clinical development times[39], and revenue forecasting[8]. Each problem poses a significant individual challenge. Incorporating all into a unified solution is critical to the decision making process. Currently, however, industry participants do not take an integrated decision making approach. Typically, they decide on project funding based on a single risk-adjusted net-present value (rNPV) estimate, assuming a fixed cost of capital[85]. This thesis will argue that this metric oversimplifies the
inherent complexities and uncertainties. This can lead to suboptimal decisions both socially and financially. A forthcoming work on optimization of pharmaceutical portfolios suggests that one reason the pharmaceutical industry is behind on quantitative decision making is because of the historical ease of drug approvals\cite{71}.

The work of Fernandez \textit{et al.} is the first academic work to combine estimates of all of these inputs with the intention of deciding how to raise funds for drug development. More broadly, there are numerous analytical and optimization works focused on the biomedical industry that deal with improving clinical trial design and selection such as adaptive clinical trial design\cite{57}, optimal trial size of a portfolio of drugs\cite{72}, optimal selection of next best trial\cite{5}, and optimal indication sequencing among many other contributions.

This thesis continues the work of Fernandez \textit{et al.} (2012) and focuses on exploring new financing models for drug-development, through the use of financial engineering. In particular, we focus on quantifying the risk profile of a portfolio of pharmaceutical projects by exploring historical industry success rates, costs, clinical/stage duration, and valuations. After extending the Fernandez \textit{et al.} model for the financing of a portfolio of pharmaceutical projects, we characterize the risk-return tradeoff as a function of the financing vehicle, and provide some examples of optimizing such a vehicle.

### 1.1 Contributions

We briefly discuss some of the major contributions of our work. A detailed discussion is deferred to subsequent parts of the thesis.

- **Model of Drug Development:** We propose novel extensions to recent work in modeling the financing of drug development including non-Markovian clinical trial times, enhanced performance measures, and new measures of correlation, each of which has a significant impact on the translational and financial performance compared to previously published work. Furthermore, we provide a first demonstration of the impact of prediction power on such models and high-
light the potential impact (stranding of drug projects) that this creates on the industry and society as a whole.

- **Drug Price Policy:** Amidst a literature review of pharmaceutical risks including costs, success rates, clinical duration, we provide new insights that connect the published works of several authors. This literature is particularly important, since it plays a critical role in the discussion of pricing policy. We believe our model and simulation framework provides a novel alternative to the usual way of addressing pricing or reimbursement policy decisions for drug development. Unlike the standard approach which ignores all uncertainty, our framework captures uncertainty in key inputs including costs, timing, success rates, and valuations. Furthermore, although the usual approach uses a simplistic cost of financing (discount rate), we instead characterize the risk-return tradeoff which depends on the structure of the financing vehicle.

- **Simulation Optimization:** We propose a novel example application (securitization) of simulation optimization under unknown constraints through recent work in Bayesian Optimization. This framework is robust to changes in modeling assumptions and may be appropriate for securitization applications more broadly.

### 1.2 Organization of Thesis

In the remainder of Chapter 1 we will first present a broad overview of current business and financing models, highlighting their differences, advantages, and disadvantages. We then provide a brief discussion of portfolio theory and securitization as it pertains to our work.

Subsequently in Chapter 2, we will discuss a model for drug development based on Fernandez et al., with an extensive discussion of the literature of estimates around historical success rates, clinical costs, trial/stage duration, and valuation that serve as inputs to the model. In particular, we provide key extensions to the original
model that serve to model reality in a number of ways, including a more detailed correlation model, potential for early cash-flows to equity (as measured by internal rate of return), and generalized distributions for clinical trial times. We show that the impact of these changes is significant economically, particularly to the timing and performance of the resulting financial vehicle.

Following this, in Chapters 3-5, we summarize three published joint works intended to provide key improvements to the model. Chapter 3 discusses the particular challenges of financing orphan diseases in addition to developing a calibrated model that suggests, given current policies, orphan drugs are a particularly attractive financial investment. Additionally the model presented therein has the potential to play a role in the discussion of orphan drug reimbursement policy due to its novel approach.

Chapter 4 highlights the added benefit of incorporating an external credit enhancement or guarantee, potentially a key component to obtaining bond ratings from a ratings agency. Without such ratings, the practical implementation of a securitization structure may be extremely difficult, since many institutional investors may be restricted to rated instruments.

Although the works of Fernandez et al. (2012) and Fagnan et al. (2013,2014) are important, they are based on literature estimates of average success. To address this, Chapter 5 demonstrates an approach using a live portfolio of drugs, constructing a model specific to the rare disease portfolio at the National Center for Advancing Translational Science (NCATS). These published results incorporate the updated performance measures and clinical trial times discussed in Chapter 2 as well as the external credit enhancement or guarantee discussed in Chapter 4.

As an alternative to securitization, in Chapter 6 we discuss joint work on a structured equity approach, and characterize the risk-return tradeoff with multiple investors with differing objectives or utility. This may be particularly important when combining philanthropic investment or in the context of longevity risk-hedging[47].

Finally, in Chapter 7 we provide some examples of optimizing the financing vehicle through bayesian optimization subject to constraints on the probability of the bond instruments, and reliance on interest coverage protection rules. We show that the
addition of debt financing can significantly increase an objective function such as the Sortino ratio for the investor, without changing the underlying portfolio.

We conclude with a discussion of our findings in Chapter 8.

1.3 Pharmaceutical Business Models

Recent discussion has suggested that the challenges and conflicts presented by a science-based business are not satisfied by the traditional business model of the industry which typically uses venture capital financing or public/private equity[75]. In this section we provide a comprehensive comparison of many of the models currently observed in practice.

Desired characteristics of various pharmaceutical business models include: independent scientific, financial, and legal oversight; access to several sources of capital (e.g. debt,equity,government,philanthropy, and the crowd); unfiltered access to the set of potential projects; the ability to take on high-risk early-stage projects with potentially poor or uncertain expected profits; and diversification of risks across dimensions including indication, modality, and collaborating organization.

1.3.1 Private Equity and Venture Capital

Since the Small Business Investment Act of 1958, venture capital or professionally managed private equity has been a cornerstone to funding early stage start-ups and new ventures. Such venture capitalists often sit on the boards of ventures they fund, retaining rights beyond mere ownership and providing management desired by their investors.

While venture capital is capable of providing valuable expertise and independent oversight, its time horizon and funding model is most appropriate for liquidity horizons of a few years[76]. In addition, sufficient diversification on pharmaceutical projects alone becomes challenging at the scale of a typical VC-fund, given the estimated average cost of more than $1 billion to develop a successful drug[73]. Indeed, some venture funds such as Polaris Partners ($3 billion under management) maintain
an equal investment in both technology and healthcare in order to provide greater
diversification and faster liquidity events.

Regardless, the overarching goal in pharmaceutical venture capital is to seek out
only the most promising projects in terms of scientific and financial potential, for
which investors typically expect high returns (e.g., a minimum of 20% expected re-
dults).

### 1.3.2 Public Equity

While public-equity has been successful at raising large amounts of capital, valuation
of pharmaceutical R&D is particularly challenging at all stages of the project
life-cycle[8], and it is unreasonable to expect a typical public equity investor to be
able to ascertain whether projects are worth continued investment[76]. Guedj and
Scharfstein (2004) suggest that smaller firms may be less willing to abandon their
only project compared to later stage firms with multiple projects, correlating to in-
creased failure of projects in Phase 2 and lower likelihood of advancing to a Phase
3 trial[34]. Financial analysts have often suggested that large pharmaceutical com-
panies should be in the business of acquiring projects, rather than doing their own
drug-discovery research[37, 42]. Pisano argues that the structure of public equity was
never designed for companies with assets largely composed of R&D, where valuation
based on earnings is unrealistic. There is little doubt that publicly traded firms are
under various pressures by investors to make particular decisions, that may be driven
more by financing than translational merit.

The added benefit to more innovative structures over traditional public equity
is the ability to diversify across all aspects of the projects, including the company
performing the research, individual career risk, and organizational structures. This is
gnouraging if the end goal is a structure in which decisions are made truly based on
the translational merit alone with financing issues secondary, influencing the nature
of the underlying financing.
1.3.3 Non-Profits and Venture Philanthropy

Non-profits and other mission-driven organizations play a critical role in the drug development ecosystem. The largest of the US charitable organizations, the Bill and Melinda Gates Foundation, maintains an endowment of $42.3 billion as of 24 November 2014, and its global health division started The Global Fund to Fight AIDS, Tuberculosis and Malaria in 2002. The Global Fund disbursed an average of $3.2 billion per year from 2009-2013[29]. Other examples within the biomedical space include the Broad Institute, which has received over $700 million in funding from the Broad Foundation. Recently, the Broad institute also received a single gift of $650 million from the Stanley Family Foundation intended to fund research on the genetics of psychiatric disorders, which is the second largest non-anonymous donation of 2014[74].

Although a significant portion of non-profit financing goes towards basic research, the focus of this thesis will be on translational and clinical medicine. During this portion of development, research is approaching, entering or completing clinical trials where non-profit organizations also play a significant role. One example includes the Leukemia and Lymphoma Society which focuses on blood cancers, and spends a portion of its budget funding clinical trials. A particularly innovative foundation is the Cystic Fibrosis foundation, which created an affiliated nonprofit named the Cystic Fibrosis Foundation Therapeutics, Inc. (CFFT) to maintain investments in a drug development pipeline across a spectrum of drugs and technologies, returning the royalties to be reinvested in the mission[27]. In addition, the foundation has also sold future royalty streams to Royalty Pharma (See Section 1.3.5), providing over $3 billion in cash and reducing its potential risk exposure due to future sales performance[79].

The Gates foundation also employed financial engineering in its transactions by appointing Lion’s Head as the fund manager for the Global Health Investment Corp. (GHIC) and offering investors a partial guarantee of up to 60% of their invested capital[28]. The fund invests in a number of projects including drugs and vaccines.
1.3.4 National Center for Advancing Translational Science

The National Center for Advancing Translational Sciences (NCATS) is the newest National Institute of Health (NIH) institute, founded in December 2011. Its mission is to “catalyze the generation of innovative methods and technologies that will enhance the development, testing and implementation of diagnostics and therapeutics across a wide range of human diseases and conditions”. Of the NCATS annual budget appropriated by Congress for 2015 ($635 million), over 74% will go towards the Clinical and Translational Sciences Awards (CTSA) program supporting a national network of medical research institutions. The remainder of the budget is spread across several initiatives within the NCATS Division of Pre-clinical Innovation. Our focus will be on two of these programs: TRND and BRIDGs, which directly support early stage drug discovery and development, and are discussed in detail in Chapter 5.

1.3.5 Drug Royalty Investment Company

Drug royalty investment companies are primarily privately owned companies that aim to acquire ownership interests in approved or late-stage pharmaceutical assets. A recent case study by Lo and Naraharisetti focused on Royalty Pharma, the largest of such companies, which was founded in 1996 by Pablo Legorreta and now manages...
over $10 billion in assets. After initial success, Royalty Pharma began to use debt-financing in 2003 and currently uses an even mixture of about $4 billion each in debt and equity significantly reducing its cost of capital. They have issued multiple tranches with varying interest rates, maturities and sizes, totalling over $3 billion, and ranging from LIBOR+2.25 to LIBOR+3% notes[45].

Royalty Pharma acquires potential assets both by reaching out to academic and research institutions and from requests from interested parties looking to sell royalties. The management team performs all research and due-diligence prior to presenting a particular project to a separate seven-person investment committee[45]. To further assess the scientific merit, patent-strength, and sales-projects, it consults key opinion leaders, clinicians, patent attorneys, specialists, doctors, investment banks and other sources[45]. In addition to diversifying its portfolio, Royalty Pharma also provides various options for sellers including synthetic or accelerated royalties[45]. Like venture capital, drug royalty investment companies have the potential to be protected against misaligned incentives such as career risk through independent oversight and decision making. At the same time, their scale, diversity and use of debt make them significantly distinct.

1.3.6 Crowd-funding

Crowd-funding is a relatively new form of funding that aims to appeal to the general public through website-based platforms. Similar to some non-profit organizations, crowd-funding often has low average donation amounts from a large number of people. According to a report by crowd-sourcing.org, the 2012 crowd-funding market raised $2.7 billion, successfully funding over a million campaigns with a forecasted increase of over 80% for 2013[51].

Although crowd-funding shares some similarities to charities/non-profits and social-networking, key differences include the ability to provide reward or investment-based funding, relatively short time horizons (weeks) to contribute, partial transparency in contribution levels of other backers, and the notion of an all-or-nothing system - contributions are often refunded if the project fundraising goal is not reached. Impor-
tantly, the contributions are not refunded if the project later fails. Recent applications include the music industry (e.g. SellaBand), independent movies, fashion designers, and many other start-ups [66]. Illustrative of the power of crowd-funding, the card game *Explo ding Kittens* designed by Elan Lee and others raised nearly $9 million during its 30 day campaign, well in excess of its goal of a mere $10,000 after reaching 1000% funded within an hour.

In the biomedical space, a number of donation-based campaign portals have focused on cancer research, and a recent study by Dragojlovic and Lynd (2014) aggregated over 125 such public campaigns[18]. They show that despite many portals with relatively low average amounts per campaign, *Indiegogo* had an average per-campaign goal of $447,938 with the second-lowest average donation of $87 among those included by the authors, suggesting that large amounts can be raised through small average donations.

Because of recent legislation through the JOBS Act, increased flexibility for equity-based crowdfunding could dramatically change the nature of crowdfunding. The implementation has been delayed by the SEC with a target date of October 2015 because of concerns with investor protection, including speculation that the crowd-funding legislation may increase the opportunity for fraud[25]. Clearly, it is unreasonable to expect the general public to possess the expertise to evaluate the scientific or financial risks of particular cancer or drug development projects.

While the JOBS Act is being finalized, Poliwogg is one example of a crowdfunding platform that targets accredited investors, allowing them to invest in private healthcare companies that run campaigns on their platform. The Poliwogg platform clearly states that its "investments are intended for investors who do not have a need for liquidity and can afford to lose their entire investment"[77].

### 1.3.7 Business Development Company

Created in the 1980s, a business development company (BDC) is a designation that allows public firms to invest in small to mid-size businesses. While similar to venture-capital or private-equity funds, they may be more accessible to smaller investors
allowing shares to be bought on the open market, allowing for potential liquidity.

Data from Closed-end Fund Advisors (CEFA) lists 51 BDC closed-end funds with combined market cap of $35 billion and an average market yield of 9.3%[49], significantly lower than that of desired VC returns. One example is the Harris and Harris Group that has elected BDC status since 1995, and invests primarily in nanotechnology companies with areas including medical devices, pharmaceutical manufacturing, drug discovery and delivery.

In the context of drug development, a BDC has immediate potential as an alternative to crowdfunding in that it may provide access to a broader range of investors; potentially increasing capital availability and efficiency. As for venture capital, BDCs have a potential for direct involvement through supervision or sitting on the board of companies in which it invests, and in fact significant managerial assistance is often a requirement. In addition, it can achieve financial benefits through diversification and leverage which could allow for a lower cost of capital.

1.3.8 Open-source Drug Discovery and Public-Private Partnerships

Recent successes in the software industry through open-source collaboration include Wikipedia, Firefox, and Linux have motivated similar approaches in drug discovery, particularly for neglected tropical diseases[61]. Similar collaboration has been achieved through various Public-Private Partnerships (PPP) such as the Medicines for Malaria Venture, TB Alliance, and International AIDS Vaccine Initiative, each with a relatively small number of staff. Notably, they are able to operate on relatively low budgets, and have achieved costs per phase dramatically lower than traditional Big Pharma for a number of reasons including using others’ unused capacity and outsourcing to developing countries[61]. Another example of a public-private partnership is the Israeli Life Sciences Fund, which resembles a typical venture capital model, with the addition of government funding to boost returns for investors by taking a first-loss position.
1.3.9 Megafund or Research-Backed Obligations

One alternative, proposed by Fernandez et al. [24], is the idea of using financial engineering through diversification and securitization (See Section 1.5) to fund biomedical products, creating what they call a ‘megafund’ or Research-Backed Obligations (RBO) structure. The megafund idea shares some similarities with drug royalty investment companies, such as Royalty Pharma, Inc., which manages billions in assets and uses approximately an even mixture of debt and equity[45]. The royalty business focuses where the risks are lower (primarily on approved royalties), while the megafund model demonstrates potential at earlier stages of drug development as well [24], where the need for financial innovation is greatest. This thesis focuses on exploring financial engineering techniques for financing structures for the biomedical industry, of which the megafund or RBO type structure are a primary example.

1.4 Portfolio Theory

Modern portfolio theory, first developed by Markowitz in 1952, formulates the tradeoff between expected return and risk for a portfolio of securities[50]. Rather than suggesting a particular portfolio, Markowitz characterized the set of efficient portfolios, or those portfolios with the lowest variance given a particular expected return. Since its development, a number of criticisms have arisen including, normally distributed returns, not taking into account higher moments of the distribution, weights can be continuous, and many others which have resulted in extensions to the original model, but will not be our focus here. Our focus will be on projects where free choice of portfolio allocation (ie., corresponding portfolio weights), may not be possible. In particular, we assume that the project must receive full funding to go forward, and that efficient (or optimal) portfolio allocation may not be possible. This leads to a non-linear dependence of return on the amount of resources allocated, which is not something modeled by the broader financial portfolio literature[46].

Although we will primarily focus on highlighting potential options in terms of risk-reward tradeoff by comparing multiple potential structures and scales, we provide an
example in Chapter 7 of choosing between such structures by optimizing a specific risk-return metric known as the Sortino ratio. The Sortino ratio was proposed as a modification of the well-known Sharpe ratio, and has been shown to be superior in the presence of skewness\cite{9}. The Sharpe ratio \((SR)\) is simply,

\[
SR = \frac{E[R_p] - r_f}{\sigma_p},
\]

the mean return of the portfolio \(E[R_p]\) subtracted by the risk free rate (or possibly another benchmark) divided by the standard deviation \(\sigma_p\) of the portfolio. The Sortino ratio, \(S\), is instead scaled by the downside semi-deviation, which we will refer to as simply downside risk,

\[
S = \frac{E[R_p] - r_t}{DR},
\]

where the downside risk (DR) is given by,

\[
DR = \sqrt{\int_{r_t}^{\infty} (r - r_t)^2 f(r)dr},
\]

where \(r_t\) is the target return.

Note that our use of the Sharpe and Sortino ratio departs from the traditional setting where returns are realized across a time-series. Instead, here we use these ratios across a single distribution which is estimated via data and models. Typically, one would fit such a distribution using historical realized returns across time. Finally, although we use the Sortino ratio as an example in this thesis, one could imagine using a different objective function depending on investor preferences. Such alternatives include the Omega ratio, upside-potential ratio, or many other custom risk-return metrics. As mentioned, we use the Sortino ratio due to its popularity and ability to differentiate between upside and downside risk.
1.5 Securitization

Securitization is the pooling of a set of assets, combined with the tranching of the resulting portfolio into slices of increasing risk. Commonly, the first tranche is referred to as the senior tranche, the second the junior/mezzanine tranche, and the final tranche is the equity tranche. In practice there may be many tranches corresponding to many levels of associated risk. Debt tranches typically are assigned a bond rating, which is provided by an independent Credit Ratings Agency (CRA) such as Moody’s Investors Service and Standard & Poor’s. Our focus in this thesis will be on cash-flow securitization (also referred to as true-sale securitization), as opposed to synthetic securitization which does not require a transfer of assets. Broadly, cash-flow securities are referred to as Asset Backed Securities (ABS), subclasses of which include mortgage-backed securities (MBS), collateralized debt obligations (CDO), and patent-backed securities (PBS).

The key players involved in securitization transactions include: the originator, a bankruptcy-remote special purpose vehicle (SPV) or issuer, servicer, and occasionally an arranger, trustee, and guarantor. The originator acquires or already owns the assets to be pooled, who then transfers the assets to the issuer (e.g. BioPharma Royalty Trust) which issues and sells the securities either privately or on the open-market. The role of the servicer is to perform the payment notifications to borrowers, generate informational reports, and monitor or manage the assets. In our context the servicer may also perform the actual research or clinical trials. The arranger is typically an investment bank, that helps design the specific tranche-levels and specifications according to investor preferences, while the guarantor provides an external credit-enhancement by guaranteeing the principal and interest payments. The servicer and originator may be the same, particularly due to shared required asset expertise. Lastly, the trustee is charged with protecting the investors and monitoring the servicer, notifying the investors of any breach of protection criteria and ensuring compliance.

1Asset backed securities are sometimes defined more narrowly as non-mortgage or collateralized debt obligation securities.
Motivation for securitization is a reduction in cost of capital, increased access to long-term capital through lower-risk institutional investors who may not otherwise be able to participate.

In addition to risks particular to certain types of securitization structures, several risks and misaligned incentives are common across any such structure. In particular, both investment managers who earn a performance fee, and may also be responsible for assembling the portfolio encouraging a risk-seeking behavior to boost expected returns, a risk referred to as *Moral hazard*.

Recently, Bugg-Levine *et al.* published an article on the Harvard Business Review discussing securitization in the context of social enterprises, suggesting the extraordinary capability of such a tool, and its ability to balance philanthropic and non-philanthropic investment. The authors discuss several recent examples of financing innovation, including loan guarantees by the Bill and Melinda Gates Foundation, pooling by Switzerland-based BlueOrchard, and social impact bonds launched in the UK. They admit that stakeholders in this sector must build the market structure to harness the power of such tools, and that this is a crucial step toward creating a greener, healthier, and more equitable world.

### 1.5.1 Financial Crisis

Although we will not discuss the crisis in detail, the type of financial engineering proposed here is related to the tools used in mortgage securities that were partly blamed for the financial crisis of 2008. Since the crisis, the SEC has taken action against 175 individuals or entities, totaling almost $2 billion in penalties; the most severe of these charges fall under the description “Concealed from investors risks, terms, and improper pricing in CDOs and other complex structured products:”[82]. Importantly, it was typically the abuse of this technology, rather than the technology itself that is the focus of the blame, suggesting preventative measures be improved. There is little doubt that if used fairly and appropriately, these tools can have an extraordinary impact. Although the structures proposed in this thesis can potentially be abused, as in the case of the crisis, we do not believe that this warrants abandoning
such a technique. Instead, we believe that with proper monitoring, transparency, and independent oversight, we can safeguard against past mistakes and mitigate risks such as moral hazard and intentional misuse.

1.5.2 Historical Examples

The idea of intellectual property (IP) and patent-backed securities has been around for at least two decades. While structurally similar to other asset-backed securities, uncertainty around the nature of the assets, patent valuation, potential risk of litigation, and risk of technological obsolescence can lead to increased difficulty. Further specific risks to securitization in the pharmaceutical industry include risk of regulatory or statutory changes.

An early example of securitization in the music industry came in 1997 when musician David Bowie issued $55 million in asset-backed securities by selling ten years of future royalties to Prudential Insurance Company offering a 7.9% interest rate with 15-year maturity[10]. The bonds were backed by about 300 songs, and a credit enhancement provided by EMI Music was needed to obtain an A3 investment grade rating by Moody’s Investor Service. This illustrates that there has long been a precedent of combining credit-enhancements in practice.

The movie industry performed at least a dozen securitization transactions from 1995-2005, ranging from $300 million to $1.1 billion in size, most of which received an Aaa rating from Moody’s[19]. These transactions include future film portfolio transactions, for which the securitization was needed to support the cost of production, which is encouraging, in that it is a practical example of securitization of assets that have yet to reach production. After performance of these deals was roughly in line with Moody’s expectations, newer structures intended to transfer more risk to investors became more popular, suggesting an increased appetite for securitization.

Recent examples of securitization in the biomedical sector include Royalty Pharma’s securitization in 2000, using only a single asset which later failed to meet expectations. Following this, Royalty Pharma issued a second securitization in 2003 using a pool of 13 drugs (only nine of which were generating royalties at the time of issuance) for
which it received an Aaa rating from Moody’s and an AAA rating from Standard and Poor’s as a result of insurance provided by MBIA Insurance Group[63]. Despite its use at later stages of development, such a securitization has yet to be performed on a portfolio including early stage assets where the financial need is greatest. In an effort to demonstrate that the typical risks could be quantified, the work of Fernandez et al. (2012) was the first publication to attempt to build a model to assess the associated risks at early stages[24]. Another recent example by Alafita and Pearce characterized the risks associated with securitization of solar power purchase agreements, assessing the impact of contract policy on securitization structures[4]. The authors proposed overcollateralization as a credit enhancement, which is simply issuing securities with face value below the value of assets, and explored the impact of policy implications on securitization structures.

The topic of applying securitization in practice even when valuation is difficult has been discussed previously, including an example by Nathan Myhrvold, co-founder of Intellectual Ventures, proposed the use of patent-backed securitization as a possibility for funding invention, envisioning an open-market for patents[62]. Finally, since at least early 2012, it has been highlighted how important such tools could be for large social problems, despite poor public perception recently[7]. This is particularly important for financing translational medicine, where non-profit financing currently plays a significant role, and could potentially be incorporated into a securitization structure.

1.5.3 Structure

This section will discuss the details of the securitization structure that is a focus of this thesis, including subordination through a standard cash waterfall approach, interest coverage ratios, amortization of tranches, and credit enhancements through external guarantees. Each tranche has a defined face value, amortization schedule (set of maturities), coupon amount, and subordination level, an example illustration is provided in Table 1.1.

Subordination, refers to the notion that higher tranches, with lower-risk, receive
<table>
<thead>
<tr>
<th>Tranche</th>
<th>Capital</th>
<th>Amortization (years)</th>
<th>Coupon</th>
<th>Interest-Coverage Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Senior</td>
<td>275</td>
<td>3.5-4.5</td>
<td>3</td>
<td>1.75</td>
</tr>
<tr>
<td>Junior</td>
<td>550</td>
<td>5-6</td>
<td>5</td>
<td>2.75</td>
</tr>
<tr>
<td>Equity</td>
<td>1925</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
</tbody>
</table>

Table 1.1: Example parameters of an RBO securitization structure using a single senior tranche, junior tranche and equity tranche. Bond amortization is done in equal parts every 6 months during the amortization period. Protection for the bonds is provided by

Figure 1-2: Depiction of cash waterfall for securitization with a single senior tranche, junior tranche and equity tranche.

cash payments for principal and interest agreements first, prior to lower tranches. Figure 1-2 depicts this for a structure with three tranches, senior, junior, and equity.

Amortization schedule refers to the repayment of principal, which in this case occurs gradually over time unlike "bullet pay" bonds which are typically paid back all at once upon maturity. For simplicity, as in the work by Fernandez et al. (2012), we will assume that repayment for each tranche occurs in equal installments from a start and end date. Typically, as in Table 1.1, we also assume that payments to principal are non-overlapping, meaning that payments to principal on a lower tranche are only allowed once all higher tranches are retired.
Potential protection mechanisms and criteria are often used to decrease risk of default. One such test is the over-collateralization (OC) test, which looks at the ratio of asset value, compared to the principal value of the current tranche and any tranches preceding it in the waterfall. Typical values range from slightly above 1 to 3. The interest coverage test, instead compares the ratio of liquid assets and tranche coupons. In our setting of research-backed securities, we will typically only include cash on hand in all coverage test checks, since the value of the asset portfolio is subject to significant uncertainty. If at any time during the life of the securitization a test is violated (i.e. not enough cash is available to meet the requirement), subsequent action to address the violation must be taken. Possible action may include partial or complete liquidation of the assets.
Chapter 2

Mathematical Model

Following the model proposed by [24], we illustrate the basic mechanisms by which diversification and financial engineering can facilitate large-scale innovation, using a stylized model of drug development. Although we start with a stylized model for intuition, we ultimately use a detailed\(^1\) Monte Carlo simulation framework to model the drug development process. In particular, suppose the R&D process for investigating the therapeutic potential of a single biochemical compound requires \(C\) in capital at date 0 and the outcome is only determined \(T\) years later. If successful, the compound will be sold at time \(T\) for an amount \(V\). In general \(T\), \(V\) and \(C\) may all be possibly-correlated random variables and could be project-specific.

For a set of \(n\) projects, we define the cost, time and values to be \(C_i\), \(T_i\) and \(V_i\) respectively. If we model the outcome of the R&D process for each project as a Bernoulli trial \(I_i\) with probability \(p_i\) of success \((I_i = 1)\) and probability \(1-p_i\) of failure \((I_i = 0)\), then the probability of at least one success in \(n\) independently and identically distributed (IID) trials is:

\[
\Pr\left(\sum_{i=1}^{n} I_i \geq 1\right) = 1 - \Pr\left(\sum_{i=1}^{n} I_i = 0\right) = 1 - (1 - p)^n . \tag{2.1}
\]

\(^1\)We attempt to validate the details of the framework through partial unit testing and external validation. It is however possible, due to the interactions of parameters and assumptions, that there are undetected bugs in the software which could impact the simulation performance. We provide an example of such testing in Appendix A.2.
In general (See Section 2.4.1) we allow for correlation among the success of trials, which we will refer to as technical correlation.

In the traditional equity model investors receive the sum of values $V_i$ for all successful projects. If we denote the number of successes as

$$N = \sum_{i=1}^{n} I_i,$$ (2.2)

the total sum of cash flows to the investor $V$ is then

$$V = \sum_{i=1}^{N} V_i,$$ (2.3)

where $N$ is a random variable.

When the project valuations $V_i$ are distributed with mean $\mu_i$ and variance $\sigma_i^2$, the expected cash to the investor is

$$E[V] = \sum_{j=1}^{N} \Pr(N = j) \sum_{i=1}^{j} \mu_i,$$ (2.4)

while the variance can be split into two terms by using the law of total variance,

$$\text{Var}[V] = E \left[ \text{Var} \left( \sum_{i=1}^{N} V_i | N \right) \right] + \text{Var} \left( E \left[ \sum_{i=1}^{N} V_i | N \right] \right).$$ (2.5)

For the case where the $V_i$ are independent and identically distributed with mean $\mu$ and variance $\sigma^2$, the total mean and variance are,

$$\text{Var}[V] = E[N] \sigma^2 + \text{Var}[N] \mu^2$$ (2.6)
$$E[V] = E[N] \mu.$$ (2.7)

When the trials are IID Bernoulli the variance simplifies to

$$\text{Var}[V] = np \left( \sigma^2 + (1 - p) \mu^2 \right),$$ (2.8)
while the mean is

$$E[V] = np \mu.$$  
(2.9)

## 2.1 Example - Single Period

In this example, investors acquire compounds prior to pre-clinical testing, and plan to sell them upon completion of phase I trials. As a result the probability of success is on the order of $p = 0.5$, see Section 2.3.1 for a detailed discussion of historical success rates. Notably, the probability of success will be much lower when carrying drugs further along the drug development process, as will be the case in some of our examples later in the thesis.

Investing in only a single project, the expected upfront cost ($C$) of trials and acquisition is about 24 million[73, 24], with a valuation ($V$) of approximately 82 million on completion of Phase I trials. As such, the annualized expected rate of return ($R$) and standard deviation of returns ($\sigma_R$) when investing in $n$ projects are

$$R = \left( \frac{pV}{C} \right)^{1/T} - 1,$$  
(2.10)

and

$$\sigma_R = \frac{\sqrt{p(1 - p)V}}{\sqrt{nT}}.$$  
(2.11)

Assuming the parameters above, with a time horizon of $T = 5$ years, for a single compound ($n = 1$) the expected return is $R = 11.3\%$ and the standard deviation is $\sigma_R = 76.4\%$. For a portfolio of 50 compounds, which requires a capital of 1.2 billion, the standard deviation becomes $76.4/\sqrt{50} = 10.8\%$.

Consider now the example of $n = 50$ compounds, where we wish to issue debt financing. Applying the binomial formula, the probability of at least 14 successes, assuming no correlation, is 99.95%, which would allow for $14 \times 82$ million $= 1.148$ billion to be paid to the debt holders after 7.5 years. Assuming a zero-coupon bond with 5% annual rate, the present value of the debt would be $1.148/(1.05)^{7.5}$ billion $= 899.5$ million. If equity was used to cover the remaining 300.5 million, the leveraged
return on equity is 24.6%, with standard deviation 43.1%. In addition, a guarantee for the debt could be purchased, which is discussed in detail in Chapter 4.

More generally, given a level of default $\delta$ we define the debt capacity $F^*(\delta)$ to be given by the solution to the equation,

$$\max_F \Pr (K < F/V) \leq \delta,$$  \hspace{1cm} (2.12)

where $F$ is the future value of the debt and $K$ is the random variable representing the number of successful projects.

### 2.2 Multi-Period Model

Of course, drugs actually have to go through a number of stages of development, each associated with increasing costs, and stage-dependent durations and probabilities of success. For the multi-period case, we start from the model developed by Fernandez et al. [24], where we define a multi-state Markov-chain with states corresponding to the phase of drug development, depicted in Figure 2-1. We make a slight modification for the clinical trial times, for which we allow a generalized distribution and use the Markov chain only to determine success outcomes. This causes an important change in the timing distributions, which were implicitly geometric in past works. Our definitions of the phases of development follow most closely to Paul et al (2010), where pre-clinical is the final stage prior to clinical studies, and is performed after earlier drug discovery including target to lead optimization. Although we do not focus on earlier stages in this thesis, the framework is flexible to do so, provided sufficient data.

### 2.3 Model Inputs

In this thesis we will focus primarily on industry-wide averages, but in practice once an originator assembles a specific portfolio, an analysis tailored to the specific set
Figure 2-1: Depiction of Markov-chain for multi-period model of drug development. Withdrawn and approval are absorbing states, and the cost, time and valuation distributions are calibrated to each state separately.

of projects would be critical. We will provide some discussion of recent work on project-level analysis and predictions, including frameworks available in practice.

### 2.3.1 Probability of Technical & Regulatory Success

A number of studies have characterized the historical probabilities of success for clinical-trials across a number of dimensions including company size, therapeutic area, source of compound, biochemical profile, stage of development, lead vs non-lead indication, and others\[13, 14, 41, 73, 15, 69, 36, 24\]. Of the recent studies included in Table 2.1, the likelihood of approval (LOA) from start of Phase 1 is from 10-19% depending on the inclusion criteria, time period, and methodology. Of these studies, only Pammolli et al. and Paul et al. provide estimates of pre-clinical success rates, and their definitions of pre-clinical may be different as Pammolli et al. do not provide a clear definition.

Although DiMasi et al. (2010) find little support of changing success rates among the 50 largest pharmaceutical firms over the time period from 1993-2004, Pammolli et al. (2011) find decreasing success rates across a broader set of companies over a similar period, which corresponds to a shift of R&D to riskier areas of development and near doubling of the fraction of small-organization projects. More recently, Hay et al. (2014) provide an extremely comprehensive set of success rates using 4451
<table>
<thead>
<tr>
<th>Source</th>
<th>Time Period</th>
<th>Number. of Compounds</th>
<th>Phase I-II</th>
<th>II-III</th>
<th>III-NDA</th>
<th>NDA-APP</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dimasi et al.</td>
<td>1993-2004</td>
<td>1738</td>
<td>71%</td>
<td>45%</td>
<td>64%</td>
<td>93%</td>
</tr>
<tr>
<td>Dimasi et al.*</td>
<td>1993-2004</td>
<td>1225</td>
<td>65%</td>
<td>40%</td>
<td>64%</td>
<td>93%</td>
</tr>
<tr>
<td>Paul et al.</td>
<td>1997-2008</td>
<td>NA</td>
<td>54%</td>
<td>34%</td>
<td>70%</td>
<td>91%</td>
</tr>
<tr>
<td>Fernandez et al.†</td>
<td>1990-2010</td>
<td>733</td>
<td>72%</td>
<td>45%</td>
<td>59%</td>
<td>95%</td>
</tr>
<tr>
<td>Kola and Landis</td>
<td>1991-2000</td>
<td>NA</td>
<td>68%</td>
<td>38%</td>
<td>55%</td>
<td>77%</td>
</tr>
<tr>
<td>Abrantes-Metz et al.</td>
<td>1989-2002</td>
<td>NA</td>
<td>80.7%</td>
<td>57.7%</td>
<td>56.7%</td>
<td></td>
</tr>
<tr>
<td>Hay et al.</td>
<td>2003-2011</td>
<td>4451</td>
<td>66.5%</td>
<td>39.5%</td>
<td>67.6%</td>
<td>86.4%</td>
</tr>
<tr>
<td>Hay et al.**</td>
<td>2003-2011</td>
<td>4451</td>
<td>64.5%</td>
<td>32.4%</td>
<td>60.1%</td>
<td>83.2%</td>
</tr>
</tbody>
</table>

Table 2.1: Success rates by clinical phase and FDA review for various studies and data time periods. * self-originated compounds ** all-indications (lead and non-lead) *** includes success or failure of NDA review. † oncology compounds

compounds, highlighting the impact of lead vs non-lead indication status impacting the results significantly.

In each of these studies, censorship occurs when trials used in each dataset have yet to advance or withdraw, and past work has shown that the expected duration of failed trials is longer which could create bias[1]. The approach taken to account for censorship includes survival analysis (or a generator matrix)[14, 24], duration modeling[1], and ignoring or justifying the potential bias[69, 36, 15]. Although Fernandez et al. (2012) used a generator matrix approach to handle censoring, they assumed time-homogeneity, an unrealistic assumption for clinical trial times, something that we address in this thesis by using generalized distributions for clinical trial duration.

Likelihood of approval and phase transition rates also vary significantly by therapeutic area. DiMasi (2010) measure that the LOA for self-originated compounds from Phase 1 ranges from 8.2% for the central nervous system (CNS) to 23.9% for systemic anti-infective[15]. Collectively, therapeutics in oncology are exceptionally low, achieving only a Phase 1 LOA of 7% according to Hay et al. 2014, and 5% according to Kola and Landis[36, 41]. Multiple studies have also documented the impact of drug class, including both lead and non-lead indications, Hay et al. find small molecules have the lowest Phase 1 LOA at 7.6%, compared to large molecules, mono-clonal antibodies, non mono-clonal proteins, and vaccines which range from 13-15%[36].

46
While cancer compounds have particularly low success rates, rare or orphan drugs have been particularly successful over the past decade. We discuss rare and orphan diseases in more detail in Chapter 3. According to Hay et al. (2014), the P1 LOA for all orphan drugs is around 33%, and as high as 44.5% for non-oncology orphan drugs. The significant increase occurs mostly at the P1 and P2 stages, and is relatively similar to non-orphan drugs at P3 and during regulatory review.

For the purposes of this thesis, we will incorporate uncertainty around the probability of success at a given phase through a Beta distribution, and in practice, one would want to further calibrate the Beta distribution to project-level factors. Following the work of Hay et al. (2014), a service has been available through BioMedTracker which provides baseline probability estimates for new clinical trials with subjective adjustments based on project-specific data with live updating.

2.3.2 Costs

Over the past three decades, two notions of pharmaceutical development costs have emerged: 1) out-of-pocket and 2) capitalized costs. Out-of-pocket costs refer only to the dollar values actually spent on clinical trials, and often even neglect fixed costs, while capitalized costs are intended to include the opportunity cost of time and the cost spent on failed drugs. A recent review article written by Morgan et al. (2011) tried to perform a systematic review of past published work, collecting thirteen published articles of which the majority had issues with confidentiality and lack of transparency, leading the authors to conclude that it is impossible to assess validity and reliability[60]. Adams and Branter (2006) seemingly claimed to reproduce the approximate findings of DiMasi et al. (2003) using public data. Unfortunately, it appears the authors re-used the survey data of DiMasi et al. and only verified the portion of the calculations arising from timing and success rates. A later work published by the same authors in 2010 attempted to address this through a new approach, estimating the marginal cost of an additional drug, but ultimately ran into difficulty recreating reasonable estimates of cost per phase[3]. Despite this, results from these published works are often used in policy discussions and have impacted
<table>
<thead>
<tr>
<th>Stage of Development</th>
<th>DiMasi et al. (2003)\cite{11}</th>
<th>Paul et al. (2010)\cite{73}</th>
</tr>
</thead>
<tbody>
<tr>
<td>Preclinical* cost (std)</td>
<td>6.8 (6.3)</td>
<td>5.4</td>
</tr>
<tr>
<td>Phase 1 cost (std)</td>
<td>20.0 (16.8)</td>
<td>16.3</td>
</tr>
<tr>
<td>Phase 2 cost (std)</td>
<td>30.9 (29.1)</td>
<td>43.4</td>
</tr>
<tr>
<td>Phase 3 cost (std)</td>
<td>113.5 (79.7)</td>
<td>162.6</td>
</tr>
<tr>
<td>NDA Submission cost</td>
<td>NA</td>
<td>43.4</td>
</tr>
</tbody>
</table>

Table 2.2: Mean costs ($ millions) for drugs entering each phase of development - adjusted to 2014 dollars using the US Gross Domestic Product (GDP) deflator.

regulation\cite{3}.

Nevertheless, capitalized costs are particularly difficult to compare, since they incorporate assumptions about costs of capital, success rates, and clinical trial times. In fact, even the out-of-pocket costs are often presented as per-approved drug, incorporating the success rate as in the review article by Morgan et al. As a result, as in Fernandez et al. (2012), we focus on estimates of out-of-pocket costs per stage, and account for impact of success, and time separately.

To arrive at these estimates, we use two primary works, DiMasi et al. (2003)\cite{11}, and Paul et al. (2010)\cite{73}. Of these, DiMasi et al. is particularly useful for our models, since it provides estimates of mean phase costs, as well as the standard deviation. DiMasi et al. have preclinical and clinical costs of $171 million USD ($87), while Paul et al. obtain $227.7 million USD for the average out-of-pocket costs for a drug completing all trials, given the standard deviation reported by DiMasi et al., these are not significantly different. Paul et al. explain that their methodology does not account for overhead costs such as salary of employees not involved in R&D but potentially necessary for the organization.

As for success rates, authors have shown significant variation across therapeutic area\cite{16}, biotech vs pharma\cite{12}, and orphan status\cite{20} (see Chapter 3 for details). Finally, public private partnerships\cite{61} and the NCATS TRND and BRIDGs program\cite{23} (see Chapter 5 for details) are able to operate on exceptionally low budgets, achieving mean phase costs up to an order of magnitude lower than typical industry costs.
Table 2.3: Clinical trial and regulatory review times (years) by phase or approximated from IND-filing date, where sources not marked use only successful trials. Dashes mark entries not provided by the authors. † does not provide transparent information on methodology. ‡ includes both successful and failed trials. * confirmed with author to include NDA filing times.

### 2.3.3 Duration

A similar body of work has been done to estimate clinical durations by stage of development and an overview of several sources is presented in Table 2.3. The most recent work by Kaitin and DiMasi calculates the total clinical times for approved drugs, as well as the regulatory filing times over the past three decades[39]. A decrease in NDA submission review times has been observed which the authors attribute to a change in the FDA review process following the Prescription Drug Use Fee Act of 1992. One issue for our methodology is that the authors do not measure the trial times for failed drugs, which have been reported to be slightly longer by Abrantes-Metz et al.[1]. Of the included sources, only those which used the Pharmaprojects database resulted in sample sizes in the thousands of compounds, due to their inclusion of failed projects and a broader scope of companies. The authors of Abrantes-Metz et al. and Adams and Brandtner (2006) also estimate the phase duration as the time between start of phase, a more appropriate input for our model. Finally, although their data from Pharmaprojects uses a similar time period, they include projects that have completed any of the phases, resulting in more recent projects being included.

Variation in clinical trial times is observed across projects[39], FDA priority status[39], orphan status[39] (see Chapter 3 for details), therapeutic area[2, 39], and market size[2]. In order to allow for project level variation, we need data on the variance
<table>
<thead>
<tr>
<th>Phase</th>
<th>Mean</th>
<th>$\mu$</th>
<th>$\sigma$</th>
<th>Range (95% Confidence)</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>1.8</td>
<td>0.212</td>
<td>0.867</td>
<td>0.30-5.14</td>
</tr>
<tr>
<td>II</td>
<td>2.8</td>
<td>0.758</td>
<td>0.737</td>
<td>0.63-7.17</td>
</tr>
<tr>
<td>III</td>
<td>2.5</td>
<td>0.621</td>
<td>0.769</td>
<td>0.5-5.59</td>
</tr>
<tr>
<td>NDA</td>
<td>1.3</td>
<td>0.018</td>
<td>0.7</td>
<td>0.32-3.22</td>
</tr>
<tr>
<td>I-ND A</td>
<td>7.1</td>
<td>1.84</td>
<td>0.5</td>
<td>2.77-14.3</td>
</tr>
<tr>
<td>I-APP</td>
<td>8.4</td>
<td>2.03</td>
<td>0.44</td>
<td>3.69-15.7</td>
</tr>
</tbody>
</table>

Table 2.4: Average duration (years) by phase and approximate log-normal parameters calibrated to obtain ranges similar to that reported by Kaitin and DiMasi[39].

by project, for which we refer to Kaitin and DiMasi. Although they don’t provide complete data or variance estimates, they provide ranges, sample size and median values. We approximately calibrate a log-normal distribution accounting for this data, assuming variance at each phase is independent. The parameters we choose are provided in Table 2.4, where we calibrate the log-normal parameters to the mean and to obtain comparable ranges as documented by Kaitin and DiMasi. Finally, we also provide plots of the probability density functions of each phase and regulatory filing time in Figure 2-2.

### 2.3.4 Valuation

The most common approach for valuation of early-stage pharmaceutical R&D projects is the discounted cash-flow or net-present value (NPV) approach, which attempts to capture all risk and uncertainty in one or more discount factors, resulting in estimation errors and unreliability[70]. A more sophisticated approach is expected or risk-adjusted net-present value, written as ENPV or rNPV. The calculation of rNPV is the sum of the discounted probability weighted cash flows,

$$\text{rNPV} = \text{NPV}(pV) - \sum_{i=0}^{n} \text{NPV}(C_i p_i),$$

(2.13)

where $p$ is the likelihood of approval, and $p_i$ is the probability of reaching stage $i$. Pandey provide an example of a negative NPV with positive rNPV illustrating the risk of adopting the simpler model[70]. However, even the rNPV approach still relies
Figure 2-2: Plot of log-normal probability density function by phase and for regulatory approval times, calibrating to obtain similar mean as in [1] and ranges as per [39].
on discounting cash-flows with subjective discount rates. Furthermore, it does not account for Jensen’s inequality that may result from uncertainty in \( T, V \) and \( C \). A simplistic approach to handling this is a more complex decision tree in addition to the rNPV approach, intended to capture some of the uncertainty around market valuation.

Another approach is real-options analysis which is based on financial option theory and attempts to take into account the value of the option to abandon. This theory typically takes into account the riskiness of the underlying asset by starting with the assumptions of the Black-Scholes equation. These assumptions are particularly unrealistic for the nature of drug development which is a prominent example of jumps in stock prices as drugs fail or succeed. Despite widespread use of such models in the financial industry, real-options analysis is not dominant in practice in the biomedical industry, due to its complexity and strong assumptions.

The model of Fernandez et al. (2012) begins by calibrating the market values from various source of approved drugs to a log-normal distribution, motivated by the observance of occasional block-buster drugs[24]. They then used a binomial-tree type approach to take into account the average probabilities of success at each phase, and discounted by qualitative risky discount rates that were agreed roughly with industry perception, ranging from 15% during NDA phase, to 30% for earlier phases. The authors further calibrated standard deviations to observed market data of market approvals, assuming the same relative variance (to the mean) at earlier phases. Finally, they used upper-bounds on the valuations based on empirical distributions. In this thesis we follow this approach, using the same discount rates as suggested by Fernandez et al. (2012).

Importantly, Fernandez et al. assume a specific deal structure that provides value upon sale of a compound that may be too optimistic; typical deal structures observed in practice favor a low upfront payment, with higher milestone payments downstream. Although we do not discuss this in detail, continuing with similar assumptions, the framework can be extended to handle more complex deal structures, accounting for the change in timing and risk, something we have explored in practice.
2.4 Modeling Dependence

We have assumed so far that the $n$ projects are statistically independent. However, in practice, even the most diverse set of projects will exhibit some pairwise dependence, reducing the diversification benefits of the portfolio and, consequently, the debt capacity $F^*$. Given the goal of securitization and the use of debt financing, dependence between projects and inputs is particularly important to the model. Although our framework can handle arbitrary correlations between each of these inputs, for simplicity we will typically only include between-project correlations which we expect to have greater impact on the tails of the entire portfolio. For example, although Abrantes-Metz et al. highlight that stage durations are correlated with project success, we will typically assume independence. We will primarily focus on correlation of success which we refer to as technical correlation (although it includes regulatory success as well), and market correlation, which we refer to as valuation correlation.

Importantly, quantitative calibration of dependence assumptions for a particular set of projects is difficult in practice. Although we believe our assumptions are reasonable for the industry more broadly and we provide a sensitivity analysis, such unknown modeling risks are not completely avoidable and provide additional motivation for the guarantee discussed in Chapter 4.

2.4.1 Technical Correlation

A simple approach used in credit modeling is to use a single common factor. If we assume each project depends on a single factor, which could represent the current scientific and regulatory setting or encapsulating the scientific review board, one such approach is a Beta-Binomial distribution. Namely, $p$ is a random variable drawn from a beta distribution $p \sim Beta(\alpha, \beta)$. We then repeat $n$ trials, resulting in $X$ successes, where $X \sim Bin(n, p)$. This formulation is intuitive, as it is simply the assumption of a beta distribution prior which is a familiar assumption in Bayesian statistics, and can be thought of as the uncertainty around the probability of success estimate. The homogenous pairwise correlation $\rho$ between projects is then $\frac{1}{\alpha + \beta + 1}$. Under the
Figure 2-3: Beta distribution with \( \alpha = \beta \) with values 4.5 (blue), 9.5 (green) and 49.5 (red), corresponding to beta-binomial correlation of 10\%, 5\% and 1\%, respectively.

resulting beta-binomial distribution the probability of observing \( k \) successes is given as

\[
Pr(X = k|n, \alpha, \beta) = \binom{n}{k} \frac{B(k + \alpha, n - k + \beta)}{B(\alpha, \beta)},
\]  

(2.14)

where \( B \) is the beta function (not to be confused with the \( \beta \) parameter or distribution).

Following the example presented in Section 2.1, with expected probability of success 50\%, Figure 2-3 shows the resulting beta distributions for correlation 10\%, 5\%, and 1\%, corresponding to \( \alpha = \beta = 4.5, 9.5, \) and 49.5, respectively. The corresponding beta-binomial distributions with \( n = 50 \) are included in Figure 2-4 in addition to the standard binomial distribution. Finally, we provide an illustration of how the debt capacity and probabilities of success for the example of Section 2.1 vary for the assumption of a Beta-Binomial corresponding to 10\% correlation in Table 2.5.

While illustrative, the beta-binomial model does not allow for varying probabilities of success \( p \), which is particularly important following the discussion in Section 2.3.1. As a result, we typically use a Bernoulli mixture model, where each project has its own distribution for \( p_i \). The simplest approach is a single-factor model, where we have a common draw \( Z \sim U(0,1) \) from the uniform distribution, and each project
Figure 2-4: Beta-Binomial distribution with $n = 50$, $\alpha = \beta$ with correlation 10% (blue), 5% (green) and 1% (red) and the standard binomial distribution (magenta).

<table>
<thead>
<tr>
<th>Number of Projects ($n$)</th>
<th>50</th>
<th>100</th>
<th>150</th>
<th>200</th>
</tr>
</thead>
<tbody>
<tr>
<td>Startup Capital ($\text{$ billions}$)</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>$F^*(1%)$ ($\text{$ billions}$)</td>
<td>0.48</td>
<td>1.12</td>
<td>1.76</td>
<td>2.40</td>
</tr>
<tr>
<td>$F^*(5%)$ ($\text{$ billions}$)</td>
<td>0.88</td>
<td>1.84</td>
<td>2.80</td>
<td>3.76</td>
</tr>
<tr>
<td>$\Pr (K \geq 6)$</td>
<td>99.37%</td>
<td>99.96%</td>
<td>99.99%</td>
<td>100.00%</td>
</tr>
<tr>
<td>$\Pr (K \geq 14)$</td>
<td>90.29%</td>
<td>99.17%</td>
<td>99.83%</td>
<td>99.95%</td>
</tr>
<tr>
<td>$\Pr (K \geq 16)$</td>
<td>85.44%</td>
<td>98.66%</td>
<td>99.72%</td>
<td>99.92%</td>
</tr>
<tr>
<td>$\Pr (K \geq 18)$</td>
<td>79.47%</td>
<td>97.96%</td>
<td>99.57%</td>
<td>99.87%</td>
</tr>
<tr>
<td>$\Pr (K \geq 20)$</td>
<td>72.49%</td>
<td>97.05%</td>
<td>99.37%</td>
<td>99.80%</td>
</tr>
<tr>
<td>$\Pr (K \geq 24)$</td>
<td>56.4%</td>
<td>94.45%</td>
<td>98.75%</td>
<td>99.60%</td>
</tr>
</tbody>
</table>

Table 2.5: Debt capacity and probability of achieving a fixed number of successes for varying project size ($n$) assuming pairwise correlation of $\rho = 0.1$ under a beta-binomial model for successful compounds. Assumptions follow the example in 2.1.
has its own marginal distribution (typically Beta) with marginal cdf $F_i(p)$. We then use the inverse transform approach for each marginal $F_i^{-1}(Z)$ to yield $n$ draws for $p_i$ from the single factor. Finally we proceed by drawing $n$ independent Bernoulli random variables to determine which projects are ultimately successful for each stage of clinical development.

More generally, we may allow for arbitrary correlation structure between projects and phases (and time if the modeler prefers). Following the copula approach, we instead draw correlated normal random variables for each project and phase, and then apply the inverse transform approach twice, first to uniform space, and then back to the desired set of marginal distributions. Although using this method may result in a different set of correlations, empirically it is close enough that we don’t worry about this difference, particularly since our correlation assumptions are quasi-empirical.

### 2.4.2 Valuation Correlation

Previously, Fernandez et al. (2012) assumed a single-factor model for valuations with homogenous pairwise correlation of 20%, based on observed correlation of equity returns of small bio-pharmaceutical firms[24]. Since we develop correlation of success separately, we also extend the nature of the correlation assumptions for valuation. For valuations alone, a 20% pairwise correlation may be a particularly severe assumption, particularly since the single-factor draw applies to all sales throughout the life of the fund which is typically 5-10 years long. We loosen this assumption by drawing a valuation factor every fixed number of periods, based on evidence that the market performance tends to be uncorrelated on a yearly scale. In practice, one would also want to measure correlation between projects based on correlation between target markets, but we will not delve into this.

Specifically, during our simulations we will draw a single factor $Y_j$ for a subset of the periods depending on the assumption. Then, the combined random draw for each project is $Z_i$,

$$Z_i = \sqrt{\rho Y_j} + \sqrt{1 - \rho} \epsilon_i,$$  \hspace{1cm} (2.15)
where $\epsilon_i \sim N(0,1)$ is the project-specific random component, and $\hat{j}$ is the closest preceding period for which we decide to repeat the common (systematic) draw. For a log-normal distribution, the valuation of project $i$ is then,

$$V_i = \exp(\mu_i + \sigma_i Z_i).$$  \hspace{1cm} (2.16)

We also explore sensitivity analysis on other distributions, transforming the correlated normal draws to arbitrary marginal distributions. As in Section 2.4.1, although this may not lead to the same correlation once inverted, it is a reasonable approximation. This model ultimately results in independence when compounds are sold farther apart in time. Of course, if the fund becomes distressed, triggering early liquidation may result in many compounds being sold simultaneously resulting in increased correlation as expected.

### 2.5 Simulation Framework

Our simulation framework broadly follows that of Fernandez et al. (2012), with the modified model laid out in this chapter, including technical correlation, generalized clinical trial times, and new measures of performance (see Chapter 5 for details). Figure 2-5 has a flow-chart of the simulation framework for illustration. The compounds are acquired during a six-month acquisition period, after which pre-clinical or the phase process begins.

At each discrete time-period thereafter (typically six months), debt and interest payments are made in accordance with the cash waterfall to meet the amortization schedule, coupon terms, and expense needs of the structure. Using the remaining cash amount, interest coverage ratios are checked, and appropriate action (partial liquidation) is taken if the conditions are not met. Compounds are then checked for transition, and are either sold upon reaching the target-phase, or funded for the next stage of development with any remaining cash, or held due to lack of available funds. Cash is initially budgeted for future development of compounds according
to a fixed budgeting rule, which is typically based on the expected success rate. Throughout the simulation, and for each compound, we draw the realized values of probability of technical success, cost of development, and stage duration for each stage of development, while allowing for possible dependence across compounds and time as discussed in this chapter.

We allow for cash-flows to equity prior to full amortization of principal on all debt tranches in cases in which excess cash arises due to sale of compounds that have reached their target development phase before the end of the transaction. Once a fixed time-horizon is reached (typically 7-10 years), we liquidate any remaining compounds at their current stages of development, using the proceeds to satisfy any remaining debt and then pay equity holders.
<table>
<thead>
<tr>
<th>Parameter</th>
<th>Preclinical</th>
<th>Phase 1</th>
<th>Phase 2</th>
<th>Phase 3</th>
<th>NDA</th>
<th>APP</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Compound valuation assumptions ($ millions).</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean</td>
<td>16</td>
<td>30</td>
<td>82</td>
<td>425</td>
<td>1,515</td>
<td>1,870</td>
</tr>
<tr>
<td>Max.</td>
<td>100</td>
<td>200</td>
<td>500</td>
<td>1,000</td>
<td>2,500</td>
<td>5,000</td>
</tr>
<tr>
<td>Lognormal mean</td>
<td>2.4</td>
<td>3.0</td>
<td>4.0</td>
<td>5.8</td>
<td>7.4</td>
<td>7.2</td>
</tr>
<tr>
<td>Lognormal s.d.</td>
<td>0.9</td>
<td>0.9</td>
<td>0.9</td>
<td>0.9</td>
<td>0.9</td>
<td>0.9</td>
</tr>
<tr>
<td>Pairwise correlation</td>
<td>0.2</td>
<td>0.2</td>
<td>0.2</td>
<td>0.2</td>
<td>0.2</td>
<td>0.2</td>
</tr>
<tr>
<td><strong>Investment assumptions ($ millions).</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Upfront</td>
<td>2.5</td>
<td>7.5</td>
<td>20.1</td>
<td>75.2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Milestone (upon completion)</td>
<td>3.8</td>
<td>10.0</td>
<td>37.6</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Development cost assumptions ($ millions).</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean expected cost</td>
<td>6</td>
<td>19</td>
<td>50</td>
<td>188</td>
<td></td>
<td></td>
</tr>
<tr>
<td>s.d. cost/phase</td>
<td>6</td>
<td>16</td>
<td>47</td>
<td>132</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Max cost/phase</td>
<td>20</td>
<td>50</td>
<td>120</td>
<td>500</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lognormal mean</td>
<td>1.5</td>
<td>2.7</td>
<td>3.7</td>
<td>5.1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lognormal s.d.</td>
<td>0.8</td>
<td>0.7</td>
<td>0.8</td>
<td>0.6</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Table 2.6: Parameters used by Fernandez et al. (2012) for their cancer megafund simulation[24].

2.6 Simulation Results

We start by illustrating the impact of our modifications on the results of Fernandez et al. (2012) using their set of parameters provided in Table 2.6. These results using generalized clinical trial times with correlated beta distributions for success rates as described in this Chapter are shown in Table 2.7. We also show the impact of allowing early payments to equity holders, by including performance measures based on the internal rate of return on the cash out-flows, resulting in average IRR values nearly twice that of the annualized return on equity value reported. This is the metric typically reported by venture capitalists, who aim for 20-25% expected internal rate of return. For ease of comparison, we provide the results for a set of all-equity based simulations without debt financing. The expected return using our updated model is slightly lower, which is a result of preventing compounds from transitioning beyond Phase 2 as was allowed by Fernandez et al. due to their discrete-time generator matrix approach.

For comparison, we also include results for a set of simulations using only pre-
<table>
<thead>
<tr>
<th>Summary Variable</th>
<th>Parameters from Fernandez <em>et al.</em></th>
<th>Parameters from Chapter 2</th>
<th>Pre-clinical only</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of Compounds</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pre-clinical</td>
<td>60</td>
<td>60</td>
<td>125</td>
</tr>
<tr>
<td>Phase 1</td>
<td>60</td>
<td>60</td>
<td>0</td>
</tr>
<tr>
<td>Research Impact</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number reaching Phase 2</td>
<td>63.3</td>
<td>67.3</td>
<td>55.78</td>
</tr>
<tr>
<td>Number sold in P3/NDA/APP</td>
<td>2.0</td>
<td>0.0</td>
<td>0.0</td>
</tr>
<tr>
<td>Equity</td>
<td>3,000</td>
<td>3,000</td>
<td>3,000</td>
</tr>
<tr>
<td>Equity Performance</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Average annualized ROE</td>
<td>7.7%</td>
<td>5.9%</td>
<td>3.4%</td>
</tr>
<tr>
<td>Prob. (return on equity &lt; 0)</td>
<td>15.6%</td>
<td>7.7%</td>
<td>23.0%</td>
</tr>
<tr>
<td>Prob. (return on equity &gt; 5%)</td>
<td>63.5%</td>
<td>58.3%</td>
<td>35.7%</td>
</tr>
<tr>
<td>Prob. (return on equity &gt; 15%)</td>
<td>17.3%</td>
<td>1.7%</td>
<td>0.6%</td>
</tr>
<tr>
<td>Average internal rate of return</td>
<td>15.4%</td>
<td>12.6%</td>
<td>5.4%</td>
</tr>
<tr>
<td>Prob. (IRR &gt; 5%)</td>
<td>74.0%</td>
<td>79.2%</td>
<td>50.3%</td>
</tr>
<tr>
<td>Prob. (IRR &gt; 15%)</td>
<td>48.1%</td>
<td>37.2%</td>
<td>9.8%</td>
</tr>
<tr>
<td>Prob. (IRR &gt; 30%)</td>
<td>16.9%</td>
<td>4.2%</td>
<td>0.2%</td>
</tr>
</tbody>
</table>

Table 2.7: Results for a simulated cancer megafund using parameters based on Fernandez *et al.* (2012), compared to results using the log-normal clinical trial times developed here, and correlated beta draws to determine success. We present an additional set of simulations in the third column, highlighting the lower performance of the pre-clinical compounds due to the assumptions of upfront payments.
clinical compounds to highlight the difference in financial performance as a result of the authors’ assumptions. In particular, the difference in assumptions suggest that buying in Phase 1 is particularly more attractive compared to buying at pre-clinical stage (even when ignoring risk levels). This suggests that the assumptions around equity stake, upfront and milestones at the pre-clinical stage may be too high, and they can be reduced to decrease the gap between stages of acquisition. For the remainder of this thesis, we will reduce the upfront of pre-clinical to zero, something that is not far from reality, particularly when we allow for 15% royalty share to the investigators.

2.7 Predictive Power and Low Budgets

In order to assess the impact of external selection on the set of projects we can potentially invest in, we provide an illustrative model of the available projects. In particular, we assume that the fund is presented with a set of possible projects that have identical costs, valuations, and durations, and success rates. Suppose now there are 125 such pre-clinical projects, with success rates drawn from IID beta distributions that are known prior to investment. We model three portfolios in Table 2-6, namely when the \( n \) projects are either the best, worst, or taken at random from the potential 125 projects. We highlight the average IRR and probability of loss as a function of the selection and number of projects \( n \). The typical venture firm invests in relatively few projects, suggesting that part of their goal is to select the best projects in order to meet investor expectations.

Under the assumed parameters, depending on the VC predictive power (or access to the best projects), their performance would lie somewhere on the line connecting the best, worst, and random points for the given portfolio size \( n \). Given the capital requirements ($550 million for 25 projects), venture capital firms are likely near the bottom of the portfolio size illustrated in Figure 2-6. Although this is a simplistic model, it captures the current financing ecosystem, in that many projects struggle to obtain financing. Despite this, financing the entire set of projects could obtain similar
Figure 2-6: Simulated performance assuming success rates for 125 projects are drawn from independent identical beta distributions and known prior to investment. The blue (yellow) curve shows the performance assuming the portfolio includes the best (worst) \( n \) projects, while the orange shows the performance when projects are indistinguishable to the investor. We also provide the performance of RBO financing (grey), assuming 5% senior debt (3% coupon) and 35% junior debt (5% coupon).

performance to a small scale VC firm, with above-random predictive power by using RBO-style financing.

As a result, we believe that this example has two important messages, the first is that it is important to be aware of the impact of predictive power on the portfolio, while the second is that, as a society it may be beneficial to prevent the best and worst projects being separately financed. Instead, we suggest that predictive power be used as a tool to manage risk, designing the appropriate financial vehicle to fund all projects (that pass scientific review), rather than to select the most financially attractive projects, potentially stranding those with lower financial performance. Finally, one only needs to look at the performance of NCATS (see Chapter 5 for details) to see that even projects that struggle to obtain traditional financing can be successful both scientifically and financially.
Chapter 3

Orphan Diseases

This chapter focuses on a model specific to orphan diseases, which play an important role in the biomedical ecosystem. In particular, this chapter summarizes joint published work with Austin Gromatzky, Roger Stein, Jose-Maria Fernandez and Andrew Lo[22]. The data-analysis was done jointly with Austin Gromatzky; the simulation modeling and result presentation were done by myself, based on a number of extensions to the original simulation model of Fernandez et al. (2012); the orphan disease project itself was initiated by Andrew Lo; parameter assumptions and simulation structure were developed with Roger Stein and Jose-Maria Fernandez, and all of the authors contributed significantly to the writing of the manuscript. We also provide separate unpublished results in Section 3.3 using the updated framework discussed in Chapter 2 for comparison.

3.1 Introduction

Drug development for rare (orphan) diseases poses additional challenges compared to non-rare drugs which include small patient populations, significant diagnostic delays, and lack of medical expertise and public awareness[81]. The legal US definition of a rare disease is any disease or condition that affects less than 200,000 persons in the United States. Although each disease may have low prevalence, an estimated 25 million to 30 million Americans are affected by a collection of more than 6800 rare
diseases recognized by the NIH. As a testament to the success of the Orphan Drug Act, in the decade prior to 1983, only 10 new drugs for rare diseases were developed by the pharmaceutical industry[64], whereas according to the FDA database, during the decade prior to November 3rd 2014, 217 orphan-designated products received FDA approval.

According to The Global Genes Project, rare diseases currently affect an estimated 350 million people worldwide and are involved in 35% of deaths within the first year of life[32]. A recent statement released by the Office of Rare Disease Research at the NIH estimates that about half of all rare diseases affect children[65].

Recent work by Fagnan et al.[22] has shown that rare diseases are particularly suitable for a megafund portfolio, benefiting from factors including faster average approval times, less expensive clinical trials on average and higher probability of success. Collectively these factors also reduce the capital required to achieve diversifying scale. Fagnan et al. (2014) demonstrate using historical performance of orphan-drugs, that 10-20 projects can yield double digit annualized returns using only $575 million dollars in capital[22].

Reimbursement for orphan diseases is particularly challenging, with drugs like Soliris that end up costing more than $400,000 per patient per year[38]. Recent work has suggested more transparency is needed around orphan drug pricing and reimbursement[84], and we believe that the work of Fagnan et al. (2014) and this thesis provide the first attempts at an absolute measurement of financial returns on orphan drugs incorporating the various forms of uncertainty related to drug development discussed in Chapter 2, something that to our knowledge has not been attempted before and should be a part of discussions around future reimbursement policy.

Finally we expect a megafund of this nature to be particularly appropriate as disease therapies become more personalized by taking into account underlying genetic mutations. For example, as recently illustrated by Lawrence et al. [43], there are dozens of mutations for many larger cancer populations, many of which occur with low frequency (10%) and are not currently considered for treatments.
3.2 Suitability for RBO financing

As discussed in Chapter 2, orphan drugs have significantly higher success rates, 22% compared to 16% for more mainstream drugs[40], and lower for cancer drugs. As an extraordinary example, protein replacement therapies for orphan diseases are estimated to have an 88% chance of regulatory approval upon entering the clinic[33]. The most recent study by Hay et al. (2014) reported approval probabilities as high as 44% for Phase 1 likelihood of approval of non-oncology orphan drugs, although these are likely upward biased due to the lookback bias created by the delay in orphan-designation[36]. The increased likelihood of success may be a result of the underlying nature of orphan diseases, the majority of which are caused by a genetic mutation that can potentially be identified and targeted[48].

Another important factor is that scientifically, orphan drug development projects are less likely to be correlated across diseases. As noted, many orphan diseases are caused by a single genetic mutation[48]. Cancers in contrast often have shared pathologies or pathways[86], suggesting a higher-potential for technical correlation. As a result, we can expect that the impact of technical correlation between orphan drug projects is particularly low. We note that there may still be valuation correlation between projects because of overlapping markets or regulatory decisions affecting orphan drug reimbursement as a whole.

From the pricing perspective, orphan drugs have been show to have comparable lifetime revenue potential to non-orphan therapies[56], in part due to their potential to receive approval for secondary indications. In particular, Thomson Reuters estimates an average orphan drug to obtain sales between US$100-500 million per year[78]. Smaller patient populations often result in high per-patient revenues. A recent example is Eculizumab or Soliris®, which is priced at more than US$400,000 per patient per year[56], for a rare blood disease called paroxysmal nocturnal hemoglobinuria.

Lastly, the availability of a 7-year marketing exclusivity increases average lifetime of a drug. According to Seoane-Vazquez et al. the extension result in a period of 11.7 years on average, corresponding to an increase of 0.8 years[83]. Of course, therapies
that receive approval late in their patent lives may have a significantly longer relative increase in marketing exclusivity.

### 3.3 Model Calibration

Following Fernandez et al. (2012)[24] and Fagnan et al. _et al._ (2013)[21], we consider an RBO transaction with a capital structure consisting of a senior tranche, mezzanine tranche and equity tranche. Because of the complexities of the waterfall and the drug approval process, numerical simulations are used to evaluate the RBO securities. We focus only on early-stage investment (preclinical and Phase I), which represents the riskiest portion of the drug-development process and where funding is scarcest. We simulate acquiring an equal number of preclinical and Phase I compounds, with the goal of selling all drugs that successfully complete Phase II trials. Our simulation relies on several key assumptions and parameters including clinical trial costs, valuations and duration of each phase (See Table 3.1).

We derive our preclinical estimates from Paul _et al._ (2012), making the assumption that the preclinical phase is similar for orphan and non-orphan drugs. Kaitin and DiMasi [39] reported that orphan drug trials in recent years take approximately 5.9 years from Phase I to NDA with an additional 0.8 years required for the approval process. The time for each phase is calculated by scaling the relationships used in [24]. Clinical transition probabilities were estimated from DiMasi (2010)[15] based on a large-molecule dataset, which we have assumed to be a close approximation for orphan

<table>
<thead>
<tr>
<th>Phase</th>
<th>Clinical Trial Cost ($MM)</th>
<th>Clinical Success Rate</th>
<th>Clinical Trial Duration (years)</th>
<th>Valuation ($MM)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Preclinical</td>
<td>5</td>
<td>69%</td>
<td>1.00</td>
<td>7.1</td>
</tr>
<tr>
<td>Phase 1</td>
<td>5</td>
<td>84%</td>
<td>1.66</td>
<td>27.6</td>
</tr>
<tr>
<td>Phase 2</td>
<td>8</td>
<td>53%</td>
<td>2.09</td>
<td>75.6</td>
</tr>
<tr>
<td>Phase 3</td>
<td>43</td>
<td>74%</td>
<td>2.15</td>
<td>321.5</td>
</tr>
<tr>
<td>NDA</td>
<td>—</td>
<td>96%</td>
<td>0.80</td>
<td>701.9</td>
</tr>
<tr>
<td>APP</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>817.6</td>
</tr>
</tbody>
</table>

Table 3.1: Simulation parameters calibrated to orphan diseases.
drugs owing to the increased targeting specificity that characterizes biologic drug development. More recently, Hay et al. (2014) found higher success rates but did not account for the timing of the orphan drug designation which may produce bias at early stages if companies only decide to file for designation amidst succeeding trials[36]. We believe the resulting success rate from preclinical to approval (21.8%) to be reasonable based on our analysis of recent orphan drugs developed by pharmaceutical companies. Valuations for each phase were obtained by discounting the estimate described above based on the probability of success and using discount rates of up to 30% per year.

Upon acquisition of compounds, we follow Fernandez et al. and assume that upfront and milestone payments are proportional to clinical costs. In addition, we increase our assumed upfront payment amounts due to the increased attractiveness of orphan drugs. Lastly, we estimate clinical trial costs using conservative values for the number of patients per clinical trial[67] and cost per patient[52]. We assume a higher cost per patient in Phase I to account for expenses associated with locating suitable candidates for the trial, which is inherently more difficult for an orphan drug.

3.4 Simulation Results - Published

We provide a summary of simulation results for orphan drugs from Fagnan et al (2014) in Table 3.2[22]. These results compare the traditional all-equity approach at two levels of capital, $374 or $575 million acquiring 10 or 16 drugs respectively, to an (approximately) optimized RBO structure at the higher level of capital. The simulation has a horizon of 6.5 years (in discrete 6-month periods), with an additional year used for the selling of compounds upon liquidation of the remaining drugs in the portfolio. The simulation attempts to sell compounds once they (successfully) complete Phase II trials, but compounds can be sold earlier in the process in anticipation of bond coupon or service payments or lack of available capital. These results use the original Markov transition style for timing of trials, resulting in geometric distributions for clinical trial duration. For comparison, Section 3.5 uses updated assumptions based on the framework discussed in Chapter 2.
<table>
<thead>
<tr>
<th>Number of Compounds</th>
<th>All Equity (Same Equity)</th>
<th>RBO</th>
<th>All Equity (Same Capital)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Preclinical</td>
<td>5</td>
<td>8</td>
<td>8</td>
</tr>
<tr>
<td>Phase 1</td>
<td>5</td>
<td>8</td>
<td>8</td>
</tr>
<tr>
<td>Research Impact</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number sold in Phase 2</td>
<td>1.1</td>
<td>2.2</td>
<td>1.7</td>
</tr>
<tr>
<td>Number sold in Phase 3</td>
<td>3.1</td>
<td>4.7</td>
<td>5.0</td>
</tr>
<tr>
<td>Liabilities</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Capital ($ millions)</td>
<td>373.75</td>
<td>575</td>
<td>575</td>
</tr>
<tr>
<td>Senior tranche ($ millions)</td>
<td>—</td>
<td>86.25</td>
<td>—</td>
</tr>
<tr>
<td>Junior tranche ($ millions)</td>
<td>—</td>
<td>115</td>
<td>—</td>
</tr>
<tr>
<td>Equity tranche ($ millions)</td>
<td>373.75</td>
<td>373.75</td>
<td>575</td>
</tr>
<tr>
<td>Equity tranche performance</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Average annualized ROE</td>
<td>10.7</td>
<td>13.4</td>
<td>11.8</td>
</tr>
<tr>
<td>Prob. (equity wiped out)</td>
<td>0.2bp</td>
<td>60bp</td>
<td>&lt;0.1bp</td>
</tr>
<tr>
<td>Prob. (return on equity &lt; 0)</td>
<td>16.1</td>
<td>13.1%</td>
<td>10.1%</td>
</tr>
<tr>
<td>Prob. (return on equity &gt; 10%)</td>
<td>54.7%</td>
<td>66.7%</td>
<td>59.77%</td>
</tr>
<tr>
<td>Prob. (return on equity &gt; 25%)</td>
<td>7.8%</td>
<td>18.4%</td>
<td>6.27%</td>
</tr>
<tr>
<td>Debt tranches performance</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Senior tranche:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>default prob., expected loss (bp)</td>
<td>—</td>
<td>0.8, &lt;0.1</td>
<td>—</td>
</tr>
<tr>
<td>Junior tranche:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>default prob., expected loss (bp)</td>
<td>—</td>
<td>56, 15</td>
<td>—</td>
</tr>
</tbody>
</table>

Table 3.2: RBO simulation results from Fagnan et al (2014) for orphan diseases using a target selling phase of Phase 3.

The average annualized return on equity for the all-equity structures is 10.7% and 11.8% respectively, which is lower than 13.4% achieved by the RBO structure. Although the RBO has an increased probability of loss (13.1%) compared to an all-equity structure using the same amount of capital (10.1%), it is lower than the all-equity structure using the same amount of equity which has a probability of loss of 16.1%. This suggests that it may be beneficial for venture capital structures to consider debt financing for orphan drugs at considerably lower levels of capital compared to the billions for cancer proposed by Fernandez et al (2012). Finally we note that the RBO structure is able to sell an additional 1.6 drugs at Phase 3, compared to an all-equity structure using the same amount of equity-capital.

A sensitivity analysis of these results can be found in Appendix A.1.
3.5 Simulation Results - Updated

For comparison to the work by Fagnan et al. (2014), we compare results using the same set of parameters, with the allowance of early cash-flows to equity. As a result, Table 3.3 shows that average internal rates of return (IRR) are approximately 3% higher than the average annualized return on equity. The second column highlights that the impact of the assumptions of Chapter 2 regarding log-normal clinical trial times significantly impact the IRR and drugs that complete Phase 2 within the time horizon (as expected), where the parameters are provided in Table 3.4. Finally, the third column incorporates the modifications to valuation and scientific correlation discussed in Chapter 2 in addition to the updated duration model. These modifications result in a slight increase to average IRR, and a decrease of about 1.5% to the probability of loss of equity. Although the probability of defaults do not change substantially, the frequency at which interest coverage ratios are triggered does increase significantly, from around 28% to 40% with the updated assumptions. Since such a high reliance on interest-coverage ratios may not be desired, we provide an example of optimizing subject to a tighter constraint on the frequency of IC coverage ratio activation in Chapter 7.

3.6 Discussion

For orphan drugs, Fagnan et al. (2014) construct portfolios of significantly smaller size than first proposed by Fernandez et al. (2012). In particular, they report results for smaller portfolios - on the order of as few as ten compounds and US$373.75 million of capital - which are able to obtain a similar risk-return profile to the larger cancer simulations. This results from the higher probability of success, lower cost of clinical trials, and faster clinical development times. This is not surprising in that it has already been observed by researchers in the biomedical literature that orphan drugs are a particularly attractive investment[56]. However, our work provides an alternative characterization of the risk-return profile for orphan drugs that has not
<table>
<thead>
<tr>
<th>Summary Variable</th>
<th>Parameters from Fagnan et al.</th>
<th>Log-Normal Stage Duration</th>
<th>Updated Correlation and Duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of Compounds</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pre-clinical</td>
<td>8</td>
<td>8</td>
<td>8</td>
</tr>
<tr>
<td>Phase 1</td>
<td>8</td>
<td>8</td>
<td>8</td>
</tr>
<tr>
<td>Research Impact</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number reaching Phase 2</td>
<td>2.18</td>
<td>2.69</td>
<td>2.68</td>
</tr>
<tr>
<td>Number sold in P3</td>
<td>4.66</td>
<td>4.29</td>
<td>4.38</td>
</tr>
<tr>
<td>Capital</td>
<td>575</td>
<td>575</td>
<td>575</td>
</tr>
<tr>
<td>Equity Performance</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Average annualized ROE</td>
<td>13.3%</td>
<td>12.9%</td>
<td>13.3%</td>
</tr>
<tr>
<td>Prob. (return on equity &lt; 0)</td>
<td>13.3%</td>
<td>14.1%</td>
<td>12.5%</td>
</tr>
<tr>
<td>Prob. (return on equity &gt; 5%)</td>
<td>78.4%</td>
<td>76.9%</td>
<td>79.3%</td>
</tr>
<tr>
<td>Prob. (return on equity &gt; 15%)</td>
<td>51.4%</td>
<td>49.0%</td>
<td>51.4%</td>
</tr>
<tr>
<td>Prob. (return on equity &gt; 25%)</td>
<td>18.2%</td>
<td>16.6%</td>
<td>16.1%</td>
</tr>
<tr>
<td>Average internal rate of return</td>
<td>16.8%</td>
<td>16.1%</td>
<td>16.6%</td>
</tr>
<tr>
<td>Prob. (IRR &gt; 5%)</td>
<td>80.0%</td>
<td>78.6%</td>
<td>80.8%</td>
</tr>
<tr>
<td>Prob. (IRR &gt; 15%)</td>
<td>60.2%</td>
<td>57.3%</td>
<td>60.1%</td>
</tr>
<tr>
<td>Prob. (IRR &gt; 25%)</td>
<td>33.5%</td>
<td>30.8%</td>
<td>31.5%</td>
</tr>
<tr>
<td>Debt tranches performance</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prob. IC ratio trigger</td>
<td>28.2%</td>
<td>40.0%</td>
<td>39.9%</td>
</tr>
<tr>
<td>Senior tranche:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>default prob., expected loss (bp)</td>
<td>&lt;0.1, &lt;0.1</td>
<td>&lt;0.1, &lt;0.1</td>
<td>&lt;0.1, &lt;0.1</td>
</tr>
<tr>
<td>Junior tranche:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>default prob., expected loss (bp)</td>
<td>53, 16</td>
<td>42, 11</td>
<td>45, 12</td>
</tr>
</tbody>
</table>

Table 3.3: Results using the parameters established by Fagnan et al. (2014) with allowance for earlier flows to equity. The second column provides a comparison with log-normal clinical trial times, and the final column includes both log-normal clinical trial times and scientific correlation following Chapter 2.

<table>
<thead>
<tr>
<th>Phase</th>
<th>Mean</th>
<th>μ</th>
<th>σ</th>
<th>Range (95% Confidence)</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>1.7</td>
<td>0.109</td>
<td>0.892</td>
<td>0.26-4.84</td>
</tr>
<tr>
<td>II</td>
<td>2.1</td>
<td>0.399</td>
<td>0.822</td>
<td>0.39-5.76</td>
</tr>
<tr>
<td>III</td>
<td>2.2</td>
<td>0.435</td>
<td>0.813</td>
<td>0.41-5.89</td>
</tr>
<tr>
<td>NDA</td>
<td>0.8</td>
<td>-0.577</td>
<td>0.841</td>
<td>0.33-1.56</td>
</tr>
<tr>
<td>I-NDA</td>
<td>5.9</td>
<td>1.63</td>
<td>0.542</td>
<td>2.09-12.43</td>
</tr>
<tr>
<td>I-APP</td>
<td>6.7</td>
<td>1.78</td>
<td>0.497</td>
<td>2.62-13.41</td>
</tr>
</tbody>
</table>

Table 3.4: Average duration by phase and approximate log-normal parameters calibrated for orphan diseases based on the same relative variance assumptions described in Chapter 2.
been explored previously. Nevertheless, although we believe their parameters to be reasonable, they are loosely calibrated and are only intended to be suggestive.

In particular, we believe that this illustrates that certain biomedical challenges can be met without reaching the scale of hundreds of projects as originally proposed in Fernandez et al. (2012). This highlights the need to calibrate the model based on the particular set of projects involved, using data to capture the specific uncertainty of the target portfolio.

Readers may be quick to claim that orphan drug pricing such as $400,000 per patient per year may not be sustainable, which may cause regulatory pressure to reduce the financial performance of orphan drugs, and our simulation results may need to be re-evaluated. Our assumptions can account for this uncertainty to some extent, by allowing for a single factor valuation correlation, which could represent uncertainty in future regulatory changes.

We show that updated results using the expanded model developed in Chapter 2 suggest similar performance for orphan drugs to that found by Fagnan et al. (2014), but with higher internal rates of return around 16-17%. Finally, we show that the additional assumptions of log-normal clinical trial times and scientific correlation significantly impact both the average and quantiles of the equity performance, in addition to the reliance on interest coverage ratios.

We believe that our simulations of orphan drugs suggest that as drugs become more targeted, larger diseases may become subdivided, resulting in treatments for smaller patient sub-populations. This is supported by the findings of Lawrence et al. who find that most cancer genes in most patients mutate with low frequency (2-20%) in larger widespread diseases, many of which are not currently explored in treatment therapies[43].
Chapter 4

Guarantee

This chapter summarizes joint published work with Jose-Maria Fernandez, Roger Stein, and Andrew Lo[21]. My role was extending the simulation framework to handle the modeling for the guarantee, in addition to contributing to the publication manuscript. An unpublished alternative pricing framework is also discussed here in Section 4.2.1, which is explored further in the next Chapter. This Chapter is particularly critical, since as discussed in Chapter 1, credit enhancements have played an important role in historical examples of securitization.

4.1 Introduction

As discussed in the first chapter, the addition of credit enhancements or guarantees may be necessary to achieve an appropriate rating for the debt, without which it may be extremely difficult to raise capital from debt markets. Although our model and simulation results suggests default probabilities comparable to the top ratings of Moody’s and Standard & Poor’s[59], rating agencies may be hesitant to give a comparable rating due to the many sources of uncertainty given the novelty of the idea. This is one notable advantage in acquiring a guarantee for the debt, and can reduce the required coupon, allow for an increase in debt and a reduction in equity. While the high bond rating and guarantee are appealing to institutional investors, and should allow for raising capital more easily, it is also beneficial to the equity
holders who will receive more leveraged returns.

The provider of the guarantee could be a government entity, but it could also be another external party interested in aiding the effort for an underlying disease such as a non-profit or mission driven organization. Of course, the guarantee does have a non-zero fair value, which should be appropriately determined. While one could guarantee the entirety of the debt, we consider the general case where the guarantee has a maximum coverage value $G$. In other words, if there are insufficient cashflows from the portfolio from successful compounds to meet the debt obligations, the guarantee will be used to cover the shortfall, up to the amount $G$.

### 4.2 Pricing

The fair price can be determined by using financial derivative pricing techniques, modeling it as a type of Credit-Default Swap (CDS). We present an estimate of this approach using a probability weighted cash-flow approach, using appropriate (risky) discount factors. As an extension, we discuss an approximated no-arbitrage approach using the risk-neutral measure, with additional assumptions. Both approaches suggest that the fair cost of the guarantee is quite low, particularly given the impact to the RBO, and the potential to take on a larger number of projects.

In the discrete-time model with $T$ discrete time periods, the cost of the guarantee $(c)$ is,

$$c = \mathbb{E} \left[ \sum_{i=1}^{T} D_i \frac{1}{(1+d)^i} \right], \quad (4.1)$$

where $D_i$ is the (non-negative) random draw on the guarantee in period $i$, and $d$ is the one period risky discount rate for cash flows. Using the simulation framework, described in Section B.3, we can estimate the cost of the guarantee by taking a sample average over all paths.

Alternatively, the guarantor may require a regular premium to pay for the guar-
an tee, in which case the fee \( f \) could be determined by setting \( c = 0, \)

\[
c = \sum_{i=1}^{T} \frac{1}{(1 + d)^i} \mathbb{E} [D_i - f I_i],
\]

(4.2)

where \( I_i \) is an indicator variable which is one if the fund has defaulted in any time period up to and including period \( i \). If we further impose that the guarantee is always drawn in full when needed, then (4.2) becomes,

\[
c = \sum_{i=1}^{T} \frac{1}{(1 + d)^i} \left( p_i G - \left( 1 - \sum_{j=1}^{i} p_j \right) f \right),
\]

(4.3)

where \( p_i \) is the probability of the draw occurring in period \( i \). For the purposes of this Chapter, we assume a no-premium guarantee in our simulations, and therefore use (4.1).

For the single (seven and a half year) period IID toy model discussed in Section 2.1, with no premium, the cost of the guarantee for the full amount of the debt is simply,

\[
c = \frac{1}{(1 + d)^T} \sum_{k=0}^{\left\lfloor F \right\rfloor - 1} \Pr(K = k) \left( \left\lfloor \frac{F}{V} \right\rfloor - k \right) V,
\]

(4.4)

which for the parameters in Section 2.1 and 2% discount rate is about 50 thousand dollars, or less than 1 bp of the face value of the debt. Of course, the cost is very sensitive to the presence of correlation between assets, which our simulation addresses in the next section.

### 4.2.1 No-Arbitrage Approach

An alternative approach is to use a no-arbitrage framework in which we discount the expected payoff of the guarantee using the risk-neutral probability distribution to compute the expectation and then discounting by the risk-free rate. Assuming that the underlying process follows geometric Brownian motion, by observing the probability \( pd_t \) of a draw on the guarantee in period \( t \), we follow Bohn and Stein (2009)[6] to convert these observed probabilities of default to risk-neutral probabilities.
of default \((pd_t^Q)\),
\[pd_t^Q = \Phi \left( \Phi^{-1}(pd_t) + \frac{\mu_a - r}{\sigma_a} \right),\]  
(4.5)
where \(\mu_a\) and \(\sigma_a\) are the drift and volatility of the underlying, and \(\Phi\) and \(\Phi^{-1}\) are the cumulative and inverse cumulative normal distribution functions respectively. We estimate the drift and volatility for the underlying from the simulated values of an all-equity structure. Finally, we use these risk-neutral probabilities to calculate a no-arbitrage upper bound for the cost of the guarantee using the deterministic bond value in period \(t\).

\[\bar{C}_Q = \sum_{t=0}^{T} pd_t^Q \max(G, P_t) \frac{(1 + r)^t}{(1 + r)^t},\]  
(4.6)
where \(G\) is the face value of the guarantee, \(r\) is the risk-free rate, and \(P_t\) is the deterministic remainder of the guaranteed bond values in period \(t\). \(\bar{C}_Q\) serves as an upper-bound on the no-arbitrage cost of the guarantee, since it assumes a recovery rate of zero on the defaulted bonds.

We note that the assumptions of geometric Brownian motion and Black-Scholes may not be appropriate, particularly if the fund does not allow for liquidity, but also because jumps are inherently characteristic of the drug-development process, and are not captured by a geometric Brownian motion model. Nonetheless, we include the approach here for comparison, and provide some examples in Chapter 5.

### 4.3 Simulation Results

We follow Fernandez et al. (2012) and simulate the addition of a credit enhancement through external guarantee, based on the model described in Chapter 2 using geometric distribution for clinical trial duration (see Chapter 5 for an updated model using the log-normal model). In this work, we focus only on the early-stage simulation-Simulation A in Fernandez et al. (2012)-which represents the more challenging portion of drug-development, where funding issues are most relevant. In Simulation A, investments in compounds that begin in the preclinical phase are sold when they transition to Phase II if they are not terminated or sold for other reasons earlier.
Table 4.1: Summary statistics of a cancer megafund simulation for all-equity (AllEQ) and debt-and-equity-financed (RBOs) cases, with (GT) and without (NoGT) guarantees of principal. 60 Pre-clinical and 60 Phase 1 compounds are acquired using $3,000 million in equity.

Table 4.1 contains a comparison of the results for 1,000,000 simulated paths for a traditional all-equity fund and a matching RBO structure, each capitalized with $3 billion of equity over seven and a half years, but in the case of the RBO structure, the fund also issues $1.25 billion of senior debt and $0.75 billion of junior debt for a total capitalization of $5 billion. The senior-tranche RBO investors received an annual coupon of 5 percent, and their principal was repaid in full 99.9 percent of the time, which is comparable to historical default rates of the highest-rated bonds reported by Moody’s[59]. The junior-tranche RBO investors were paid an annual coupon of 8 percent and repaid in full 99.6 percent of the time; and equity-tranche investors received an average annualized return of 9.1 percent. In over a third of the simulated sample paths the average annualized return for equity exceeded 15 percent, versus only about a sixth for the case of the equity only fund.

While the all-equity fund exhibits only a modestly lower probability of negative
returns than the RBO equity tranche, it also exhibits a substantially lower probability of very large returns as can be seen in the comparative probabilities of returns exceeding 15 percent. Of course, the most significant impact of the RBO structure is that it brings almost twice as many compounds-103 versus 63-to Phase II as the all-equity fund due to financial leverage.

With the addition of a third-party guarantee, with the assumption that there are no additional fees or payments, the capital structure can be altered in a number of ways while still preserving the credit risk profile of the bonds. Table 4.1 reports results for a pair of simulation experiments, A1 and A2, that resemble Simulation A, but in each case, the capital structure is altered to increase the proportion of senior debt by reducing a portion of the more-difficult-to-place securities. In Simulation A1 a capital structure is chosen that reduces the fraction of capital allocated to equity and increases the fraction in the senior tranche, while in Simulation A2 we remove the mezzanine tranche entirely, leaving a capital structure allocated only between equity and senior debt. In both cases, we start with total capital of $5 billion and a guarantee with a maximum face value of $1 billion and report the comparable no-guarantee results to highlight the impact of the guarantee. Not surprisingly, the results in Table 4.1 show that credit losses are substantially higher without the guarantee. However, the less obvious result is that the expected cost of the guarantee to the provider is small relative to the amount guaranteed, with an expected loss of 0.1 to 1 percent of the face value of the guarantee. In fact, it is likely to be much less than the face value as demonstrated in the extreme quantiles in Table 4.1. These results suggest that even a small (in expected value) third-party guarantee can materially improve the economics of an RBO transaction.

As with any numerical simulation, the results in Table 4.1 depend on the various input parameters such as cost, revenue, and transition-probability assumptions, each of which can be debated at great length.
Chapter 5

NCATS Portfolio Analysis

This chapter summarizes joint published work with Nora Yang, John McKew, and Andrew Lo[23]. The data-collection was done by Nora Yang in consultation with John McKew and myself. Valuation panel respondents were assembled by Andrew Lo, who were provided data by Nora Yang influenced by discussions with myself. The data analysis and simulation calibration was done by myself with discussions with Nora Yang to establish strength of prior belief weights. Finally the simulation modeling and results were done by myself. This work was the first to publish the impact of log-normal clinical trial times and alternative measure of performance such as internal rate of return. We note that the internal rate of return is measured slightly differently here than the model discussed in Chapter 2, the details of which can be found in Appendix B.

5.1 Introduction

We simulate a realistic rare-disease megafund using data from projects accepted by the NCATS Division of Pre-clinical Innovation (DPI). In particular, we look at rare disease projects from the Therapeutics for Rare andNeglected Diseases (TRND) and Bridging Interventional Development Gaps (BrIDGs) programs. This study is interesting for three reasons. First, we provide updated parameters for use in simulation of rare diseases. In addition to traditional data sources for assumptions about quan-
tities such as costs, timelines, and success rates, we also convened a panel of experts to evaluate the past and current NCATS portfolio of rare diseases. By combining this data with industry literature estimations from Fagnan et al. [22] for typical orphan diseases, we establish a modified set of parameters to estimate performance of an NCATS based megafund.

Second, we provide an updated simulation framework that allows for general distributions of clinical trial timelines. Third, we provide an informative metric for measuring RBO performance. Although average annualized returns assuming constant horizon liquidation range from 12-16%, we demonstrate that average internal rates of return (IRR) measured on net cash-flows, a metric often used by venture capitalists, can be more than twice the raw annualized returns. The NCATS data suggests significantly lower costs, increased success rates, and longer pre-clinical timelines. We find that simulated performance of an NCATS rare-disease megafund is comparable in IRR to venture capitalist preferences of over 25% IRR. The addition of debt tranches and a guarantee can result in an average increase in raw returns of twice the initial equity investment. Finally, we note that although we model the NCATS mega-fund as a private enterprise, further benefits could be obtained from a public-private partnership model.

5.2 TRND and BrIDGs Overview

The TRND program within the NCATS Division of Pre-clinical Innovation (DPI) considers applications for projects in the space of translational medicine where the target disease must qualify for either US Food and Drug Association (FDA) orphan designation or the World Health Organization (WHO) neglected tropical disease list. In an industry where collaboration can be difficult, TRND brings together NIH scientists and resources to applicants who can be academic scientists, nonprofit organizations, or pharmaceutical and biotechnology companies.

In addition to academic experience, DPI researchers have experience with drug development and have previously worked at dozens of companies across the industry
including Pfizer, GlaxoSmithKline, Amgen, Genentech, Merck and the US Food & Drug Association (FDA), TRND offers access not only to their staff, but also their drug development capabilities and clinical/regulatory resources. In fact, in some cases TRND even contributes to new innovations leading to jointly held intellectual property through work on areas such as process chemistry.

Applicants to TRND undergo a thorough application and evaluation process after which the collaborators provide starting points and expertise on a particular rare disease and are admitted to a milestone-driven drug development program. TRND admits projects throughout the pre-clinical pipeline, of which most begin by performing an Investigational New Drug (IND) enabling study. One advantage of this business model is TRND’s ability to avoid financial impact or incentives impacting project termination, allowing them to focus on pre-determined milestones. TRND has taken projects into the clinic, completing both Phase 1 and Phase 2 studies. Their goal is to take projects to a stage where they are attractive to biotechnology and pharmaceutical companies who are able and willing to aid in later-stage clinical development.

The TRND program also explores innovations aimed at improving preclinical success rates, reducing risk and costs of advancing research breakthroughs into treatments. TRND focuses on the gap between basic discovery and testing new drugs in humans by primarily generating data for successful Investigational New Drug (IND) applications and first-in-human studies.

The BrIDGs program also focuses primarily on generating data for IND applications, but is not limited to rare diseases. Eligibility is limited to academic institutions, not-for-profit organizations, and small businesses. As with TRND, BrIDGs is not a grant-based program and successful applicants are provided with clinical resources and NIH contractors at no cost. Project segments are typically performed sequentially, where subsequent segments are only initiated once the preceding segments have completed successfully.
### 5.3 TRND Project Identification and Selection

TRND applications are accepted in batches and are reviewed by a committee of experts in drug development for scientific merit and technical feasibility. After undergoing a pre-screening during which data requirements are discussed, applicants submit a data package and supplemental materials. Following this, TRND senior staff assign a few reviewers to each project, who perform an in-depth evaluation of preclinical potential based on the data package. TRND then requests additional data as necessary, and arranges a face-to-face meeting to assess collaborative potential. A final balanced portfolio that fits with NCATS overall mission is then proposed by program staff.

Applications are evaluated based on a weighted set of five criteria, which is outlined in Table 5.1. In addition, committee members also rate the strength on a number of other dimensions including toxicology, medicinal chemistry, in vivo models, as well as several others.

<table>
<thead>
<tr>
<th>Application Criteria</th>
<th>Criteria Weight</th>
</tr>
</thead>
<tbody>
<tr>
<td>Target and therapeutic validation</td>
<td>30%</td>
</tr>
<tr>
<td>Strength of current data package</td>
<td>30%</td>
</tr>
<tr>
<td>Feasibility to reach first-in-human status</td>
<td>20%</td>
</tr>
<tr>
<td>Medical impact relative to current standard of care</td>
<td>10%</td>
</tr>
<tr>
<td>Likelihood of external adaption</td>
<td>10%</td>
</tr>
</tbody>
</table>

Table 5.1: TRND application criteria and weights.
5.4 Data Analysis

Data was collected for all rare-disease projects from both the TRND and BrIDGs programs within the NCATS DPI. The resulting data included 28 rare disease projects, 13 of which were from the BrIDGs program, and 15 from the TRND program. The portfolio spanned a diverse range of therapeutic areas: only 3 of the projects were within oncology, while the other projects included 5 hematology, 5 musculoskeletal, 2 cardiovascular, 6 central nervous system, 3 endocrine, 2 ophthalmology, and 1 respiratory. Of the projects, 5 were existing drugs repurposed for orphan diseases, 13 are new molecular entities (NME), 8 large molecules, 1 stem cell therapy, and 1 gene vector. In addition, the collaborating organization varies across the sample, including 15 academic, 9 small biotech companies, 3 NIH, and 2 large pharmaceutical companies. As such, despite a small sample size, they represent a diverse group in terms of therapeutic area, modality, and collaborating organization.

The dataset includes 20 active projects, motivating measurement at intermediate milestones to capture the depth of the data. Milestones were established including Lead Optimization, Investigational New Drug (IND) enabling, IND filing, Phase 1 and Phase 2. Of the 28 rare disease projects, 24 entered the NCATS pipeline at the IND enabling phase, and four in the Lead Optimization phase. Sources of data included clinical and regulatory success of observed transitions between established milestones, durations of such transitions (including time spent active and on hold), and costs paid for by NCATS, NIH and other project collaborators during each transition period. This procedure resulted in 10 transitions from IND enabling, 4 from IND filing, 2 from Phase 1 and a single transition from Phase 2. We further increase the number of observed transitions by including projects that were continued by collaborators after completion of the BrIDGs program. This resulted in an additional 5 measured transitions from Phase 1, and 3 from Phase 2. Because of the small number of observations (4-10 per phase), we apply Bayesian style weights (using expert views) to update estimates based on literature estimates for orphan drugs from Fagnan et al. (2014). In order to make a fair comparison, we combine the two IND phases, which
we relate to the pre-clinical phase in Paul et al (2010)[73].

5.5 Valuation Panel

The past works discussing the RBO or megafund structure have relied on average data or literature estimates within a specific disease category. While illustrative, a practical implementation of such a structure would use project specific estimates that take into account the specific drug success rates, patient population, and intellectual property potential. A valuation panel of five experts was contacted and asked to provide valuation estimates of 28 rare-disease projects undertaken by NCATS. The five panel members are currently active in the biotech industry, and have a mixture of past experience in biotech venture capital, drug development, investment-banking and consulting. Their current roles vary from CEO, founders, managing partners and vice-presidents. Respondents were asked to estimate the fair market value for each project in its current state. Each respondent was given the option to provide up to three estimates, a low valuation, best-guess valuation, and a high valuation. Their responses were independent, and minimal direction was provided on how they should complete their task. They were given no financial incentive to perform the task. Their estimates are provided in Table 5-1.

For the majority of the projects, the best guess of at least two panelists were higher than the corresponding estimates from the literature using only phase information. The values of one panelist for some projects were orders of magnitude higher than the other respondents. To reduce the impact of these outliers and improve the accuracy of our estimates of market value, we use the median estimates among the five panelists rather than the maximum (which is what a typical bidding process would do). Finally, we capture the imprecision of valuing early stage biotech projects by specifying a large standard deviation (over 80% of the value of the mean) for the distribution from which we draw our valuations in our simulation.
5.6 Simulation Calibration

The simulation model used in Fagnan et al. (2014) relies on several key model inputs, including clinical trial costs, clinical trial durations, market valuations, and probability of technical and regulatory success. In order to calibrate a set of parameters for prospective simulations of an NCATS megafund of rare diseases, we take a weighted average of the NCATS observations and literature estimates of Fagnan et al. (2014) using weights based on prior beliefs and intuition about the NCATS process. For example, we expect higher success rates, lower costs and longer pre-clinical duration due to the NCATS application process and lack of performing things in parallel. Finally, we use the median panel valuations to estimate average market valuations for NCATS rare disease projects by phase. The observations, literature estimates and impact are shown Figure 5-2.

The impact of these calibrations results in lower costs and higher success rates for all phases, longer pre-clinical development times, shorter clinical development times, and lower valuations. The impact is greatest at the pre-clinical phase where we have
Figure 5-2: Simulation calibration: weighted averaging of parameter estimates based on NCATS rare disease portfolio, valuation panel and literature estimates[22], using prior belief weights (details provided in the Appendix B).

the greatest number of observations, and is small at phase 2, where we have observed fewer transitions. In addition to these key inputs, there are many other inputs such as correlation, standard deviations of costs and valuations, distribution models, upfront and milestone payments and equity sharing. These numbers and methodology are discussed in the Supplemental Information section. With these additional data and assumptions, we calibrate log-normal distributions for the project costs, valuations and durations.

5.7 Simulation Setup

We use the approach presented in Chapter 2, including the option of a third-party guarantee as discussed in Chapter 4. We employ the detailed calibration discussed in the last section, leveraging the framework developed for orphan diseases in Chapter 3. We model the NCATS portfolio as a hypothetical private-sector megafund, ignoring any potential public-private partnership benefits, and also ignoring the value of
new intellectual property such as general translational medical expertise and patents generated by NCATS staff independently or jointly with collaborators. Following Fernandez et al. (2012) and Fagnan et al (2013), we consider an RBO structure consisting of a senior tranche, mezzanine tranche, and an equity tranche.

We focus on early-stage investment, simulating the sale of pre-clinical projects upon completion of Phase 2, if successful. In addition to the calibration of inputs discussed in the previous section, we employ the more realistic model for stochastic clinical times using a log-normal distribution discussed in Chapter 2, abandoning the Markov-chain approach used in previous studies which implicitly imposes a geometric distribution. Appendix B.4 provides a sensitivity analysis for other distribution assumptions.

5.8 Simulation Results

The results of three sets of simulations using the NCATS rare-disease-portfolio calibrated parameters are shown in Table 5.2, with each set based on 2 million simulated paths. Each set of simulations acquires solely pre-clinical compounds with the intent to carry the compounds through completion of a Phase 2 trial. The first set of simulations consists of an RBO structure in which the senior and junior debt tranches are assumed to pay 5% and 8% semi-annual coupon rates, respectively. Using capital of $420 million ($189 million in debt, $231 million in equity), 16 pre-clinical compounds are acquired and funded. The second set of simulations consists of an all-equity structure in which 9 pre-clinical compounds are acquired using a similar amount of equity capital ($230 million) as in the first simulation. The third set of simulations is similar to the RBO, but contains the added feature of a third-party default guarantee for the junior debt tranche, protecting the principal of these bond holders in case of default. This guarantee has the effect of shifting the junior debt tranche into the senior tranche, yielding a single (senior) debt issue for the RBO structure. All three simulations use a maximum 11-year horizon, including a 6-month setup time, and 1 year for terminal liquidation of projects.
<table>
<thead>
<tr>
<th>Summary Variable</th>
<th>All Equity (Same Equity)</th>
<th>RBO</th>
<th>RBO with Guarantee</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of Compounds</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pre-clinical or IND-Enabling</td>
<td>9</td>
<td>16</td>
<td>16</td>
</tr>
<tr>
<td>Research Impact</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number sold in Phase 2</td>
<td>0.4</td>
<td>1.9</td>
<td>1.6</td>
</tr>
<tr>
<td>Number sold in Phase 3</td>
<td>3.4</td>
<td>5.3</td>
<td>5.6</td>
</tr>
<tr>
<td>Liabilities</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Capital ($ millions)</td>
<td>230</td>
<td>420</td>
<td>420</td>
</tr>
<tr>
<td>Senior tranche ($ millions)</td>
<td>—</td>
<td>105</td>
<td>189</td>
</tr>
<tr>
<td>Junior tranche ($ millions)</td>
<td>—</td>
<td>84</td>
<td>—</td>
</tr>
<tr>
<td>Equity tranche ($ millions)</td>
<td>230</td>
<td>231</td>
<td>231</td>
</tr>
<tr>
<td>Guarantee ($ millions)</td>
<td>—</td>
<td>—</td>
<td>100</td>
</tr>
<tr>
<td>Equity tranche performance</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Average raw ROE</td>
<td>3.25</td>
<td>5.14</td>
<td>5.32</td>
</tr>
<tr>
<td>Average IRR</td>
<td>26.7%</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>Average MIRR (0% refinancing)</td>
<td>18.3%</td>
<td>21.6%</td>
<td>22.7%</td>
</tr>
<tr>
<td>Average annualized ROE</td>
<td>11.6%</td>
<td>14.7%</td>
<td>15.4%</td>
</tr>
<tr>
<td>Prob. (equity wiped out)</td>
<td>1.3bp</td>
<td>0.52%</td>
<td>0.34%</td>
</tr>
<tr>
<td>Prob. (return on equity &lt; 0)</td>
<td>8.0%</td>
<td>6.2%</td>
<td>5.1%</td>
</tr>
<tr>
<td>Prob. (return on equity &gt; 10%)</td>
<td>61.9%</td>
<td>76.8%</td>
<td>78.6%</td>
</tr>
<tr>
<td>Prob. (return on equity &gt; 25%)</td>
<td>2.2%</td>
<td>10.4%</td>
<td>11.0%</td>
</tr>
<tr>
<td>Debt tranche performance</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Senior tranche:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>default prob., expected loss (bp)</td>
<td>—</td>
<td>0.1,</td>
<td>&lt;0.1, &lt;0.1</td>
</tr>
<tr>
<td>Junior tranche:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>default prob., expected loss (bp)</td>
<td>—</td>
<td>50, 15</td>
<td>—</td>
</tr>
<tr>
<td>Guarantee performance</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prob (cost of guarantee &gt; 0)</td>
<td>—</td>
<td>—</td>
<td>0.3%</td>
</tr>
<tr>
<td>Expected cost, 2% discount ($)</td>
<td>—</td>
<td>—</td>
<td>65,000</td>
</tr>
<tr>
<td>No-arbitrage cost of guarantee ($)</td>
<td>—</td>
<td>—</td>
<td>110,000</td>
</tr>
</tbody>
</table>

Table 5.2: RBO performance for one all-equity structure, one senior/junior tranche structure, and one guaranteed senior tranche structure. Each structure acquires only pre-clinical compounds with a target goal of reaching Phase 3 and a maximum horizon of 11 years.
In addition to the performance metrics used in Fagnan et al. [4], we include two other metrics to provide a more detailed comparison. Motivated by industry practice, we include the mean raw return, with no discounting performed (e.g., a mean raw return of 2.0 would mean that for every $1 of equity capital committed, an average of $3 is returned at the end of the simulation). In addition to the internal rate of return (IRR) for the all-equity simulation, we include the Modified Internal Rate of Return (MIRR) on net cash flows, where the financing rate for negative cash flows is set to zero. The MIRR is computed by fixing the financing rate at zero and solving iteratively until the average MIRR rate equals the (forward) reinvestment rate. For details on this calculation, see Appendix B.

Table 5.2 shows that the average annualized return on equity for the all-equity model is 11.6%; this corresponds to a significantly higher IRR of 26.7%, due to the chance of earlier cash flows and without the assumption of holding cash which may not be realistic in practice. By adding senior and junior debt of $105 and $84 million, respectively, the average annualized equity return is increased to 14.7%, with a corresponding MIRR of 21.6%, which is higher than the 18.3% MIRR for the all-equity model. It should be noted that, while useful for comparison, the MIRR may not be a realistic performance measure for a structure with debt since the full amount of capital may need to be held as collateral. A sensitivity analysis of these results is provided in Appendix B.

Table 5.2 also shows that the default risk to the bonds is quite low, with less than 1 basis point (bp) default rate on the senior tranche, comparable to the historical performance of bonds with the highest credit ratings. Ignoring discounting, the average benefit to equity holders of adding debt is an almost two-fold increase over the initial equity investment.

As a result of increased scale, the probability of loss to the equity tranche using the RBO structure is only 6.2%, compared to 8.0% for the all-equity model. The addition of debt also increases the chance of annualized returns in excess of 25% by a factor of nearly 5. The clinical impact is also increased, resulting in an additional 1.9 projects completing Phase-2 trials compared to the all-equity model using a similar
level of equity.

A further increase in returns can be obtained by the addition of a third-party guarantee of $100 million, presumably provided either by a government agency or philanthropic organization. Specifically, we consider a guarantee that has the effect of combining the two debt tranches in one single senior tranche paying a 5% coupon rate. In addition to potential fundraising benefits and higher bond-ratings, the impact to equity returns is significant, increasing the average annualized return on equity to 15.4%. Despite the high face value, the expected discounted cost to the guarantor is quite small at $65,000, with an estimated Black-Scholes price of $110,000 (see Chapter 4.2.1 for details).

A sensitivity analysis of these results is provided in Appendix B.4, where we conduct the same simulation experiments under a variety of different parameter values. One illustrative example is a 15% relative decrease in success probabilities at each phase, which causes the simulated return on equity for the RBO to drop from 14.7% to 10.6%, still an attractive investment in the current economic climate. Moreover, under this alternate specification, the default risk to the senior bond does not increase while the junior bond default rate increases by only 18bp.

5.9 Discussion

Although the simulation results presented in Fagnan et al. (2013, 2014) are promising, a megafund structure has yet to be implemented in practice. In their work, Fagnan et al. (2015), analyze a live rare disease portfolio within the TRND and BrIDGs programs at NCATS, which has been active for at most 4 years at the time of analysis, and is therefore still preliminary. Nevertheless, the combination of NCATS data and industry averages provide further evidence that such a structure has potential. These simulations also aim to illustrate the realized benefits of the megafund business model including independent scientific review and pre-defined project continuation/termination criteria.

The simulations of Fagnan et al. (2015) show that a rare-disease megafund based
on the NCATS business and operation model could achieve average annualized returns from 12 to 15% depending on the debt structure and with substantially higher internal rates of returns. The addition of a guarantee to the debt, similar to that discussed in Chapter 4, can increase the number of drugs funded for the same level of equity, the return on equity, and the ability to raise debt financing. In particular, the average impact of adding guaranteed debt to the traditional all-equity model, reported by Fagnan et al. (2015), is an increase in the total cash payout to equity holders of twice their initial equity investment.

We note that these simulations are not yet backed by data of market sales of approved drugs, which have yet to be produced by the NCATS portfolio. Despite this, one-third of the projects included have obtained independent private funding despite struggling to obtain such financing when they submitted their application to NCATS. As further encouraging evidence, two collaborating companies were also acquired by larger pharmaceutical companies, which had one-day stock gains of $238 million and $423 million for Baxter and Shire, respectively. This provides evidence that even projects that struggle to obtain private financing at early stages, can pass rigorous scientific review, early stage clinical trials, and ultimately attract private financing once passed the so-called valley of death.

Given the high variance of the panel respondents, in practice one would likely want to repeat this process with greater incentives for accuracy by panel respondents either by asking them to place real bids or by providing payment for a more detailed analysis. As a result, these simulation results are intended to be illustrative rather than a precise estimate of future performance. Another concern may be that early projects taken on by NCATS are extraordinary successful due to backlog, and that project performance may decline over time, which is something that management would need to monitor and assess, recalibrating the simulation inputs as necessary.
Chapter 6

Structured Equity

This section discusses on-going work done in collaboration with Roger Stein. My contribution includes the optimization models and examples presented here, code for simulations, and mathematical derivations.

While debt financing is particularly well suited to the application of RBO structures due to the trillions of available capital and patience of investors in this sector, practical challenges have slowed the implementation of a RBOs as a mechanism for drug discovery. In particular, in order for the debt to be issued, investors, ratings agencies and guarantors would all potentially need to understand the details of the business model and mathematical assumptions underlying it. Nevertheless, the ideas in this thesis extend beyond securitization, by connecting differing objectives of potential investors. To address this challenge, we explore an alternate approach that we term structured equity and which preserves some of the attractive features of debt issuance without necessarily requiring some of these implementation hurdles. To that end, we explore new mathematical models and simulation performance for a variety of structures using structured equity. In particular, we show that by creating structures that pay out based on the number of successful projects, or based on the magnitude of sales, that we can tranche investments in both risk and time.
6.1 Structured Equity Model

In previous works the megafund securitization model relied on debt issuance which allows for a significantly greater pool of capital from investors for whom even after diversification traditional equity remains unattractive due to the investment horizon or the risk. Here we present a general framework for structured equity with the goal of bridging the gap between the novelty of using debt to tranche risk and maturity and lack of flexibility from traditional equity models. In particular, we explore the potential of using structured equity which allows investors the option of multiple equity pieces, each with different risk profiles.

For simplicity, our model assumes that each structured equity piece provides a portion of the required up-front capital used to fund the projects, and that the investors receive cash outflows upon the sale of every successful project. Under this setting, with \( m \) equity pieces, each piece provides an up-front nominal amount \( S_k \), \( k \in (1, 2, \ldots, m) \), where the total up-front equity is \( S \),

\[
S = \sum_{k=1}^{m} S_k, \tag{6.1}
\]

for which the holder receives a series of cash flows based upon the valuation and success of the projects.

Although a variety of equity structures is possible, we will focus on a few examples and discuss the motivations and limitations of each. We first make the distinction between two types of uncertainty, technical uncertainty which impacts the number of successful projects, and valuation uncertainty which affects the financial valuation of a successful project. In the context of Equation 2.5, the first term is due to valuation uncertainty while the second arises from technical uncertainty.

By assigning these types of variability differently to each equity piece, we hope to attract a greater variety of investors. We consider two key tradeoffs for a scheme, structure complexity and flexibility. We start with a few linear schemes where the equity holder receives a linear proportion from each individual success, or collection
of successes. The sum of cash flows (terminal value) upon completion to the holder of equity piece \( k \) is denoted \( V^k \), while \( V_i \) remains the value of project \( i \) if successful.

The typical case or traditional equity model corresponds to linear weights,

\[
V^k = \sum_{i=1}^{n} \frac{S_k}{S} V_i, \tag{6.2}
\]

where the weights, \( w_k = \frac{S_k}{S} \) correspond to the fraction of up-front capital provided by the investor.

Our first example of a structured equity case is one in which the number of successes are ordered by their time to completion, and the linear weights are assigned in this order. We will refer to this scheme as ordered success. In this case the sum of cash flows upon completion is,

\[
V^k = \sum_{i=1}^{N} w_i^k V_{[i]}, \tag{6.3}
\]

where the \( V_{[i]} \) is the value of the \( i \)-th ordered success, not simply the \( i \)-th project, and \( N \) is the random number of successful projects. Under the case where success of the projects are i.i.d Bernoulli, \( I \) is distributed Binomial\((n,p)\). In general, technical correlation between the project successes could be handled similar to Chapter 2. Under this scheme, this terminal value distribution is a mixture distribution, where the mixing probabilities are given by the probability mass function of \( N \) and the distributions are a weighted sum of the (dependent) random variables corresponding to valuation of individual projects. In the absence of valuation uncertainty (i.e. deterministic \( V_i \)), this scheme aligns the technical risk (ie. the number of successes) with the weights and, as a consequence, risk can be stratified efficiently. See Section 6.2 for an example of this setting.

However, when valuation uncertainty is significant, this scheme subjects equity holders to the variation of individual project valuations and is hence not pareto-optimal for all parties. We provide an example highlighting this sub-optimality in Section 6.3.
More generally, the scheme could be a general function of the values produced from sales of compounds, reducing the sub-optimality. On the other hand, parties may be particularly keen to take on this risk, in order to hedge external risks such as longevity risk[47]. Naturally, annuity writers exposed to longevity risk may wish to hold the equity tranche with weights only in the later successes, since this would provide a perfect hedge for the additional risk provided by a resulting cure.

6.2 Example - IID Deterministic

Under the setting with deterministic costs, valuations and timing, we assume investment in $n = 16$ projects, using the same setup as in Chapter 2, for pre-clinical through completion of Phase 1. In particular we assume projects are IID Bernoulli with probability $p = 50\%$, $T = 5$, $C = \$24$, and $V = \$82$ for all projects. If we create a structure of two equal equity pieces receiving the exit valuation cashflows from 8 projects each, with the first piece receiving $w^1_i = 1$ for $i \in \{1, 2, 3\}$ and $w^1_i = 0.1$ for $i > 3$, and $w^2_i = 1 - w^1_i$, then the annualized mean returns are

$$E[R_{1,2}] = \left( \frac{\sum_{i=1}^{N} V w^1_i \Pr(K \geq i)}{16C} \right)^{1/T} - 1, \quad (6.4)$$

where $K \sim$Binomial$(n,p)$ is the number of successful projects. This yields annualized expected returns of 8.4% for the first tranche, and 14.0% for the second. To receive a positive return, tranche 1 needs at least three successes, and tranche 2 needs 6 successes, which occur with probabilities 99.8% and 89.49% respectively. As a result, the first tranche may be more suitable to a risk-averse investor. Note that in the multi-period setting, the first few successes would be discounted less, since they would occur on average faster, resulting in higher average IRR.
6.3 Example - Valuation uncertainty sub-optimality

In the presence of uncertainty in $V$ (variance $\sigma^2$), sub-optimality in terms of the risk-return tradeoff can occur with the ordered success structure proposed. Consider the extreme example where $p = 1$. In this case, the setup is equivalent to the well-known portfolio theory example where tranche 1 holds weights $w_1^i$ and tranche 2 holds weights $w_2^i$ in a linear portfolio of assets with mean $V$ and variance $\sigma^2$. Under that setting, given that the projects are assumed to be IID, the optimal weights are necessarily equally weighted suggesting that any ordered success scheme would produce sub-optimality for both tranches. In general, the sub-optimality will depend on the level of valuation uncertainty and probability of success $p$. We provide a richer example in Section 6.4 through the simulation framework presented in Chapter 2.

6.4 Simulation Results

We present simulation results for three levels of valuation uncertainty, based on a relative scaling of the standard deviations used in Fagnan et al. 2014[22]. The simulation acquires an equal number of Pre-Clinical and Phase 1 compounds depending on the scale. The first set, compares the ordered success structure to two traditional equity models - one with the same total capital, and one with the same high-risk equity capital. For the structured equity case, we assign 90% of the value of the first two successes and 5% of additional successes to the low-risk equity piece, with the remainder going to the high-risk piece.

Figure 6-1 compares performance metrics for the structures, including average internal rate of return (IRR), average annualized return on equity (ROE), and probabilities of low/high IRR. Figure 6-1a highlights the expected IRR values which lie between 15-20%, while Figure 6-1b shows the previously reported metric of annualized ROE assuming payout only at horizon, which is significantly lower around 9-14%. This is due to the high potential of early cash-flows on the sale of compounds during the simulation.
(a) Average internal rate of return.  
(b) Average annualized return on equity.  
(c) Probability of equity loss.  
(d) Probability of $\text{IRR} \geq 20\%$.  

Figure 6-1: Simulated performance metrics comparing traditional and structured equity. The blue/gray lines are traditional equity at 8 and 16 compounds, respectively. The yellow/red lines are low/high risk equity pieces using an ordered success scheme that acquires 16 compounds.
As expected, the High-Risk structured equity piece has the highest expected IRR and ROE, with a 10-16% relative increase in the probability of over 20% IRR depending on the valuation uncertainty as shown in Figure 6-1d. The impact to average IRR is an increase of about 0.5% compared to the same total capital, and 2-3% compared to the same level of high-risky equity. This illustrates that venture capital firms who raise a fixed amount in high-risky equity, can benefit by increasing scale and adding a lower-risk equity piece.

Figure 6-1c shows that at high levels of uncertainty (1.0 scaling), both the low and high-risk structured equity pieces have a probability of loss higher than traditional equity at the same scale. This demonstrates the sub-optimality of the linear weighting scheme, which subjects both pieces to the risk of individual sales, as in our earlier example in Section 6.3. One could imagine more general structures that also depend on the realized values of successful projects, which would start to look like preferred equity.

6.5 Discussion

In this chapter we have shown that an alternative approach to securitization could be taken, by structuring multiple equity tranches with different risk levels. This may allow for an increase in the potential sources of capital, allowing investors with higher or lower risk appetites to participate. In particular, since securitization has proved slow to implement in practice due to the breadth of topics, an structured equity approach may be easier to implement, while still providing some of the advantages. We show that using a simple linear ordered success scheme may result in sub-optimality, particularly as valuation uncertainty becomes large.
Chapter 7

Optimization of Financing and Transaction Structure

This chapter provides a practical overview of optimizing over the financial structures discussed in this thesis. This is particularly important to implementation of the structure in practice, since investors may want to optimize their risk-return tradeoff, or may need to enforce constraints on the frequency of reliance on protection rules that were triggered quite frequently by the authors in Fernandez et al.[24] and Fagnan et al.[21]. We provide examples of optimizing over parameters previously published, and show that significant gains in Sortino ratio can be obtained, in addition to reducing the reliance on interest coverage (IC) protection rules.

Given a calibrated set of simulation outputs, a practitioner would like to optimize over a set of decision variables including the mixture of phases acquired, how much to budget for the future cost of compounds, what capital structure to use, when to sell compounds, and how to tranche the capital structure. Furthermore, they may wish to select where they lie on the risk-return frontier by optimizing over an objective function such as the Sortino ratio presented in Chapter 1.

Although one could imagine solving a complete dynamic programming problem to determine when to buy and sell compounds, we instead search only over a heuristic subset of policies that are simple to implement. This is motivated by the fact that it may be difficult to enforce more complex policies, which is essential when using
securitization. As a result, we typically employ a few simple rules regarding budgeting for future compounds, when to liquidate part of the portfolio, and when to allow early cash-flows to equity holders. Previously, the selection of the parameters for these rules has mostly been done via a grid search, but as the number of dimensions (capital structure, budgeting rules, payment rules) increases, an alternative is necessary. The potential dimensions that could be optimized, are the budgeting rules, capital structure, business rules such as interest coverage ratios, or structured equity weighting schemes.

Bayesian optimization emerged as a method for global optimization of expensive functions in 1978, first pioneered by Mockus et al.\cite{Mockus1978}. Recent work in Bayesian optimization\cite{Snoek2012} has been extended to handle unknown constraints which are only known upon realization (e.g., running a simulation or experiment). In particular, they also allow for noise in the constraint evaluation, and demonstrate improved performance compared to a comparable large penalty approach.

For our simulation framework, we hope to solve,

$$\max_x f(h(x, y))$$

subject to

$$PD_i(x, y) \leq \epsilon_i \quad \forall i \in (1, 2, \ldots, n_b) \quad (7.1)$$

$$pc(x, y) \leq \epsilon$$

where \(y\) is fixed and embeds all underlying assumptions, \(x\) has any decision variables controlling the portfolio setup and projects, \(f\) is a user-defined objective function that embeds risk-reward tradeoff preferences such as the Sortino ratio, \(h(x, y)\) is the simulation framework outputting performance metrics such as the internal rate of return or annualized return on equity, \(PD_i\) is the probability of default of tranche \(i\), \(\epsilon_i\) is the maximum allowed probability of default, \(n_b\) is the number of bond tranches, \(pc\) is the probability of selling early due to interest coverage protection rules, and \(\epsilon\) is the maximum allowed probability of selling due for interest coverage. We evaluate \(h\), \(PD\), and \(pc\) through our simulation framework discussed in Chapter 2.

As a result, this creates an extremely flexible approach in that it allows for the
capability to add any number of business rules or model assumptions, without changing the framework or underlying mathematics. This allows for a general framework independent of correlation structure, mathematical representation of the simulation framework or assumptions regarding distributions. Although there is some theory on convergence for specific acquisition functions for the unconstrained case, in general theory is limited. Nevertheless, we find it particularly useful in practice for our problem setup since we are only interested in approximate optima.

7.1 Numerical Results

For a simple 2-d optimization, we show the results of applying the framework Spearmint based on the paper of Gelbart et al. (2014)[31]. In particular, we use the same setup described for Figure 2-6, using a capital amount of $2650 million, and optimizing the fraction of senior and junior debt, holding everything else fixed. We optimize the Sortino ratio, assuming the equity holder has a target return of 10%, and we constrain the frequency of selling caused by interest coverage rules to 1%, and the senior debt to have a default probability at most 5 basis points. We typically submit jobs in parallel, running each parameter set selected by Spearmint for 5000 simulation paths, which is enough to get a reasonable estimate (typically the sample average IRR is within a few percent of the true mean), but is significantly less than would be needed for a precise estimate of the tail or default probabilities. The resulting objective function is shown in 7-1, which shows two resulting local minima using either senior or junior debt exclusively. Either resulting choice lies roughly on the probabilistic constraint controlling the interest coverage rule. This is encouraging, since the structures reported by Fernandez et al. (2012), and Fagnan et al. (2013,2014) resulted in significant reliance on these coverage rules, for example approximately 19% of sample paths in Simulation A of Fernandez et al. resulted in early selling of at least one compound due to interest coverage rules. The Sortino ratio and performance metrics are provided in Table 7.1.

For a second example, where we combine an even mixture of Pre-clinical and
Figure 7-1: Plot of the Gaussian prior mean using a Sortino ratio objective function targeting a return of 10%. 125 Pre-clinical projects are acquired and sold upon completion of Phase 1, using the setup described in Chapter 2. The axes are the fraction of the junior and senior debt, which are constrained to a maximum of 50% arbitrarily in order to narrow the search space. The shaded circles are the sampled points after sampling 65 times, and the star represents the best single simulation run, which is not necessarily significant.

<table>
<thead>
<tr>
<th>Structure</th>
<th>Mean IRR</th>
<th>Downside Risk (10%)</th>
<th>Sortino Ratio (10%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All-Equity</td>
<td>10.4%</td>
<td>0.047</td>
<td>0.093</td>
</tr>
<tr>
<td>Junior-Debt (28%)</td>
<td>11.2%</td>
<td>0.054</td>
<td>0.214</td>
</tr>
<tr>
<td>Senior-Debt (15%)</td>
<td>10.8%</td>
<td>0.048</td>
<td>0.175</td>
</tr>
</tbody>
</table>

Table 7.1: Sortino ratio, mean internal rate of return, and downside risk using a target return of 10% for three structures: an all-equity structure with no debt financing, a junior-debt (5% coupon, amortized equally over 3 periods from year 5) structure using 28% debt, and a senior-debt (3% coupon, amortized equally 3 periods from year 3.5) structure using 15% debt. 125 Pre-clinical compounds are acquired at the start of the simulation using $2650 million.
Figure 7-2: Plot of the Gaussian prior mean using a Sortino ratio objective function targeting a return of 10%. 60 Pre-clinical and 60 Phase 1 projects are acquired and sold upon completion of Phase 1, using the setup described in Chapter 2. The axes are the fraction of the junior and senior debt, which are constrained to a maximum of 50% arbitrarily in order to narrow the search space. The shaded circles are the sampled points after sampling 96 times, and the star represents the best single simulation run, which is not necessarily significant.

Phase 1 projects as in Fernandez et al. (2012) and we again optimize over the senior and junior debt fractions. Figure 7-2 shows the resulting objective function surface, while Figure 7-3 shows the surface of the constraint limiting the frequency of selling due to interest coverage protection rules. We provide the performance metrics for the optimized RBO structure (34% senior debt, 8.5% junior debt), compared to the all equity in Table 7.2.

7.1.1 Optimizing Fernandez et al. (2012)

As an additional example, we optimize over leverage for the early-stage simulation of Fernandez et al. (2012). Before doing so, however, we note that Fernandez et al. (2012) stressed that their numerical simulations were intended only as proofs of concept, highlighting the need for more robust optimization in practical settings. Table 7.3 shows that the Sortino ratio of the annualized return, with a target return of 8%,
Figure 7-3: Plot of the Gaussian prior mean of the constraint controlling the probability of selling for interest coverage. The x markers represent sampled points that failed to meet the constraint, while the circles satisfied the constraint. The parameters and setup used are the same as in Fernandez et al., with the modifications discussed in Chapter 2.

<table>
<thead>
<tr>
<th>Structure</th>
<th>Mean IRR</th>
<th>Downside Risk (10%)</th>
<th>Sortino Ratio (10%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All-Equity</td>
<td>15.6%</td>
<td>0.031</td>
<td>1.78</td>
</tr>
<tr>
<td>RBO (34% senior, 8.5% junior)</td>
<td>19.4%</td>
<td>0.037</td>
<td>2.54</td>
</tr>
</tbody>
</table>

Table 7.2: Sortino ratio, mean internal rate of return, and downside risk using a target return of 10% for three structures: an all-equity structure with no debt financing, a junior-debt (5% coupon, amortized equally over 3 periods from year 5) structure using 28% debt, and a senior-debt (3% coupon, amortized equally 3 periods from year 3.5) structure using 15% debt. 60 Phase 1 and 60 Pre-clinical compounds are acquired at the start of the simulation using $2900 million.
Table 7.3: Sortino ratio, mean annualized return on equity, and downside risk using a target return of 8% using parameters from Fernandez et al. (2012). The results of optimizing the Sortino ratio of annualized return on equity through bayesian optimization (BO) are compared to the structure proposed by the authors. Two optimizations are performed, each with at least 50 samples, with no IC constraint and a 1% IC constraint, respectively.

<table>
<thead>
<tr>
<th>Source</th>
<th>Senior Debt</th>
<th>Junior Debt</th>
<th>Mean ROE</th>
<th>Downside Risk (8%)</th>
<th>Sortino Ratio (8%)</th>
<th>Pr (IC)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fernandez et al.[24]</td>
<td>25%</td>
<td>15%</td>
<td>9.1%</td>
<td>0.097</td>
<td>0.111</td>
<td>19%</td>
</tr>
<tr>
<td>BO (no IC constraint)</td>
<td>27%</td>
<td>2%</td>
<td>9.2%</td>
<td>0.069</td>
<td>0.177</td>
<td>4%</td>
</tr>
<tr>
<td>BO (1% IC constraint)</td>
<td>22%</td>
<td>0%</td>
<td>9.0%</td>
<td>0.063</td>
<td>0.162</td>
<td>1%</td>
</tr>
</tbody>
</table>

can be significantly increased using a reduced amount of both junior debt. This is not too surprising, since the work of Fernandez et al. only attempted approximate optimization of annualized ROE without a quantitative tradeoff of risk. This new capital structure achieves a 9.2% annualized ROE, slightly above 9.1% for the structure proposed by the authors, who only used an approximate optimization using a coarse grid search. In addition, it achieves a Sortino ratio (of annualized ROE) about 60% higher than Fernandez et al. (2012), while triggering IC ratios about a fifth of the time. In addition, we perform a second optimization with a tightened IC constraint (1%), which may be a more realistic assumption than that of recent published works, since it is possible some investors might it more attractive to invest in structures in which the protection rules are triggered less frequently. This results in a significant decrease in the amount of debt used, and a slight decrease to the Sortino ratio from 0.177 to 0.162, which is still well above the Sortino ratio of Fernandez et al. (2012), Of course, different objective functions or target returns will result in different optimal structures.

We also provide an illustration of the impact of allowing for early-cash flows to equity as described in Chapter 2 in this thesis. Instead in Table 7.4 we optimize the Sortino ratio of internal rate of return, which we have argued can be significantly higher and may be more appropriate for equity investors. Again we are able to obtain significantly higher Sortino ratios by optimizing, while reducing the reliance on the IC protection rules. We note however, that Fernandez et al. (2012) did not allow
Table 7.4: Sortino ratio, mean internal rate of return, and downside risk using a target return of 8% using parameters from Fernandez et al. (2012). The results of optimizing the Sortino ratio of internal rate of return through bayesian optimization are compared to the structure proposed by the authors. The optimizations is performed with at least 50 samples, with no IC constraint.

<table>
<thead>
<tr>
<th>Source</th>
<th>Senior Debt</th>
<th>Junior Debt</th>
<th>Mean IRR</th>
<th>Downside Risk (8%)</th>
<th>Sortino Ratio (8%)</th>
<th>Pr (IC)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fernandez et al.[24]</td>
<td>25%</td>
<td>15%</td>
<td>16.2%</td>
<td>0.107</td>
<td>0.77</td>
<td>34%</td>
</tr>
<tr>
<td>BO (no IC constraint)</td>
<td>18%</td>
<td>0%</td>
<td>15.5%</td>
<td>0.065</td>
<td>1.16</td>
<td>0.3%</td>
</tr>
</tbody>
</table>

Table 7.5: Sortino ratio, mean internal rate of return, and downside risk using a target return of 12% using parameters from Fernandez et al. (2012). The results of optimizing the Sortino ratio of annualized return on equity through bayesian optimization (BO) are compared to the structure proposed by the authors. Two optimizations are performed, each with at least 50 samples, with no IC constraint and a 1% IC constraint, respectively.

<table>
<thead>
<tr>
<th>Source</th>
<th>Senior Debt</th>
<th>Junior Debt</th>
<th>Mean IRR</th>
<th>Downside Risk (12%)</th>
<th>Sortino Ratio (12%)</th>
<th>Pr (IC)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fernandez et al.[24]</td>
<td>25%</td>
<td>15%</td>
<td>16.2%</td>
<td>0.124</td>
<td>0.342</td>
<td>34%</td>
</tr>
<tr>
<td>BO (no IC constraint)</td>
<td>21%</td>
<td>3%</td>
<td>15.9%</td>
<td>0.089</td>
<td>0.432</td>
<td>0.9%</td>
</tr>
</tbody>
</table>

for earlier cash-flows to equity, so their structure is not optimized for internal rate of return.

The internal rates of return are over 50% higher than the annualized ROE metrics, due to the significant chance of receiving cash flows earlier than the end of the simulations. For this setup, the IC constraint was not binding at 1%; a result of the lower level of debt used compared to Table 7.3 for annualized return. Finally, we provide results in Tables 7.5 and 7.6 for the same set of optimizations using a target IRR of 12% and 15%, respectively. As expected, the optimal debt fractions increase with higher target IRR, as does the mean expected internal rate of return, and downside risk, leaving it up to the investors’ preference to select a target return. As the target return and optimal leverage increase, the interest coverage protection rules again become an important constraint to consider, as illustrated with a target IRR of 15% in Table 7.6. Although tightening this constraint results in a lower sortino ratio, it may be desirable since it is less likely to trigger interest coverage protection rule which may be difficult to enforce in practice.
<table>
<thead>
<tr>
<th>Source</th>
<th>Senior Debt</th>
<th>Junior Debt</th>
<th>Mean IRR</th>
<th>Downside Risk (15%)</th>
<th>Sortino Ratio (15%)</th>
<th>Pr (IC)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fernandez et al. [24]</td>
<td>25%</td>
<td>15%</td>
<td>16.2%</td>
<td>0.138</td>
<td>0.089</td>
<td>34%</td>
</tr>
<tr>
<td>BO (no IC constraint)</td>
<td>28.5%</td>
<td>4.4%</td>
<td>16.3%</td>
<td>0.115</td>
<td>0.108</td>
<td>5%</td>
</tr>
<tr>
<td>BO (1% IC constraint)</td>
<td>22%</td>
<td>3.4%</td>
<td>16.1%</td>
<td>0.105</td>
<td>0.105</td>
<td>1%</td>
</tr>
</tbody>
</table>

Table 7.6: Sortino ratio, mean internal rate of return, and downside risk using a target return of 15% using parameters from Fernandez et al. (2012). The results of optimizing the Sortino ratio of internal rate of return through bayesian optimization are compared to the structure proposed by the authors. The optimization is performed with at least 50 samples, with no IC constraint.

7.2 Discussion

In this chapter we have highlighted the impact of optimizing over an objective function such as the Sortino ratio to match investor preferences. In particular, we show that constrained Bayesian optimization as developed by Gelbart et al. [31] is a viable methodology due to its ability to account for noise in both the objective and constraints. With around 50 function evaluations, or samples, of simulations (each with 5,000 simulation paths) we are able to find solutions which outperform published structures, which were not optimized for risk-return tradeoff.

We highlight that the contributions of Chapter 2 that allow for earlier cash-flows to equity result in internal rates of return about 50% larger than annualized rates of return. This difference results in significantly different optimal capital structures. Finally, we have shown that for some parameter settings, the amount of debt may cause a significant reliance (10-30)% on interest coverage ratios. We show that this can be controlled by constraining the dependence on such rules, resulting in a modest reduction of the optimal Sortino ratio (<10%) in the case of Fernandez et al. (2012)[24].

In general, we may desire to perform optimizations with more decision variables, such as the coverage ratios and payout rules, both of which would impact the impact of the IC constraint as well as the risk-return tradeoff. Further constraints could also be added, such as sensitivities to certain parameter assumptions, which may be particularly useful in practice.
Chapter 8

Conclusions

Since Mary Lasker began fighting for cancer research funding and the declaration of the war on cancer with the National Cancer Act in 1971, public funding has played a large role in the funding of basic biomedical research. It is a serious concern that in the last decade a reverse in the trend of the NIH budget has occurred. The financing of translational medicine has also struggled and has recently been referred to as the “valley of death”. Despite this, the National Center for Advancing Translational Science has shown above-average success rates when selecting from rare-disease projects that are unable to otherwise obtain financing. Furthermore, these same projects have then been able to obtain financing once passing early clinical trials, or the so called valley of death. The current ecosystem for financing at pre-clinical and early clinical stages relies primarily on venture-backed biotech companies and venture philanthropy through non-profit organizations and foundations. We demonstrate, based on historical success rates, costs, valuations, and clinical trial duration, that funding models that utilize financial engineering techniques such as diversification and securitization may be particularly suitable to address these challenges.

We extended the model developed by Fernandez et al. (2012) to account for generalized clinical trial times, technical correlation, and additional measures of performance to account for the potential of early cash flows to equity. These additions dramatically change the timing of the cash flows previously published, and suggest internal rates of return nearly double the annualized numbers corresponding to sin-
gle equity payouts previously reported by Fernandez et al. (2012) and Fagnan et al. (2013, 2014). These additions significantly impact the number of projects reaching a target phase, and the feasibility of the underlying debt structure which requires a specific timing of principal and interest payments.

Although it has been shown that typical success rates and clinical durations of the largest pharmaceutical companies have remained relatively stable over the last two decades, there is substantial variation depending on therapeutic area, drug modality, and company type. As a result, we believe our parameters and distributions are reasonable, and we encourage readers to download our software and use their own assumptions. Finally, we note that in practice, project-specific estimates would be important to account for such variation.

A key limitation of our model is that it is difficult in practice to quantitatively calibrate the level of dependence or correlation for particular set of projects. Although we believe our assumptions to be reasonable, such modeling risks will always exist, providing additional motivation for the guarantee to protect the bond holders from such risks. Nevertheless, a sensitivity analysis of some of the assumptions suggests that the default rates of the senior bonds are not overly sensitive to many of the underlying parameters and assumptions due to protection rules and the availability of cash if projects fail early. Additionally, the deal structures assumed in this thesis are simplistic, and in practice would need to be calibrated to market assumptions in terms of the portion of value given as upfront, milestone, and royalties, particularly at early stages of development.

The implications of our model suggest that venture capitalists (with limited budgets) are incentivized to select projects with high scientific and financial performance, which may increase the difficulty of funding projects that are less financially attractive. Ideally, as a society we would like to ensure funding for all translational projects which meet a set of scientific quality criteria, as has been done at the National Center for Advancing Translational Sciences (NCATS). Through the use of diversification and securitization a *megafund* could access a greater pool of capital and fund less attractive projects while maintaining an attractive risk-return profile. We suggest
that this motivates the use of a scientific review panel similar to Royalty Pharma or NCATS to select projects with appropriate scientific merits. A secondary financial review panel could then assess the financial performance of the particular projects using our methodology, and a financial vehicle could be constructed to employ efficient (or optimal) financing. This is distinct from current industry practice, which often combines the scientific and financial information during the selection process, resulting in many projects that go unfunded.

We demonstrate that the addition of a guarantee can benefit both debt and equity holders by allowing for increased flexibility in the financial structure. Ultimately, such a guarantee may be necessary to obtain the appropriate debt rating to attract institutional investors such as pension funds, sovereign wealth funds, endowments, and foundations. We demonstrate two potential uses, allowing for a reduction in equity (and increased returns), or removal of the junior debt tranche, both of which may increase the ability to raise required capital.

As an example of the dependence of model parameters and inputs across disease areas, we calibrate a model specific to rare or orphan diseases, which we argue are particularly suitable to the tools of financial engineering despite smaller patient populations. These results suggest that orphan drugs are a particularly attractive investment due to their increased chance of success, faster average approval times, lower clinical costs, and enhanced market exclusivity. This has been previously reported by Meekings et al. (2012) although we provide an alternative characterization by formulating specific estimates of the rates of return, for example 10.7%[22] for an all-equity structure compared to 7.9% for a comparable cancer fund[24]. We further demonstrate this by using a live portfolio of rare-disease projects that have experienced milestones at the National Center for Advancing Translational Sciences, which have obtained higher than average success rates, lower clinical costs, and longer pre-clinical duration compared to the literature estimates for average orphan drug projects[22].

Motivated by practical difficulties in starting a large securitization structure in practice, we show that similar benefits can be obtained through structured equity design, to accommodate differences in investor objectives. We show an example struc-
ture by splitting risks based on ordered successes, and discuss potential sub-optimality in terms of risk-return tradeoff.

Finally, we provide specific examples of optimizing an objective function, the Sortino ratio, through Bayesian optimization with constraints on the probability of default on the debt and the reliance of the interest coverage protection rules. In particular, we show that the resulting Sortino ratios are significantly increased compared to previous published structures, even at the same scale of capital. Of course, further benefit can be obtained if there are budget constraints on the amount of equity capital.

We believe that a future structure for funding translational science could achieve increased separation of decision-making based on translational merit and finance; where projects are advanced or stopped primary based on translational merit alone. Financial analysis or predictive forecasting can then be used to design or adapt the vehicle, to maintain accordance with capital requirements and restrictions. Finally, we believe that there is a large untapped potential in profit-based crowd-funding, that could become viable as the SEC finalizes the regulations surrounding the JOBS Act. This could allow for significantly reduced cost of capital, which could translate into reduced prices for drugs or higher royalties for basic research, rather than simply toward investor returns.

Although this thesis focuses solely on financing for drug-development, a similar approach could be used for financing other large-scale social initiatives with potential for financial return and sources of funding that vary in their utility or objective. The characteristics we rely on are primarily social need, large capital requirements, potential for financial return, the ability to quantify and model the associated risks, and differences in investor preferences.
Appendix A

Orphan Supplementary Materials

A.1 Orphan Sensitivity Analysis\textsuperscript{1}

In this section, we show results to illustrate the sensitivity to megafund scale (number of compounds, capital), asset correlation, and clinical success rates.

In Figure A-1, we present a comparison of the RBO (solid blue line) to the all-equity structure (dotted black line) for increasing correlation from 5\% to 40\%. We approximately optimize the RBO structure at each level of correlation. Panel d) shows the optimized leverage for the RBO structure which increases with lower correlation. Panel c) shows that the probability of high returns (> 25\%) for the all-equity structure increases with correlation since diversification diminishes. This effect is reversed for the RBO structure, since it is out-weighed by the impact of decreasing leverage. Panel (a) shows the average return on equity for both structures, where we observe under high correlation the models approach one another. Finally, panel b) shows the chance of a loss of equity under both structures.

Note that the ROE changes for the equity-only case in the figures because at each correlation level, the equity amount and number of compounds purchased are adjusted to match the capital amount in the RBO. The equity amount in the RBO may be different because the capital structure of the RBO is quasi-optimized for performance at each correlation level. The changes in capital structure can be observed clearly in

\textsuperscript{1}\text{This section was published as the supplementary materials of Fagnan \textit{et al.} (2014)[22].}
Figure A-1: Comparison of approximately optimized RBO structure (solid blue line) with an all-equity structure (dotted black-line) for pair-wise asset correlation ranging from 5% to 40%. Compounds are intended to be sold upon completion of Phase 2 trials.

Panel (d), in which both the optimized percentage of debt and the relative mix of senior and junior debt are shown at different levels of correlation.

Figure A-2 compares the RBO (solid blue line) to the all-equity structure (dotted black line) for increasing scale from 6 to 100 compounds, where again we optimize the RBO capital structure at each scale. Panel d) shows the optimized leverage for the RBO structure which increases with scale. Panel c) shows that the probability of high returns (>25%) for the all-equity structure decreases with scale since diversification diminishes. This effect is reversed for the RBO structure, since it is out-weighed by the impact of increasing leverage. Panel a) shows the average return on equity for both structures, where we observe for low scales the debt capacity shrinks and the structures are the same. Finally, panel b) shows the chance of a loss of equity under both structures, which is modestly higher for the RBO structure at all scales.
As before, the ROE changes for the equity-only case in the figures because at each portfolio size level, the capital amount and number of compounds purchased are adjusted to match the capital amount in the RBO. The equity amount in the RBO may be different because the capital structure of the RBO is quasi-optimized for performance at each portfolio-size level. The changes in capital structure can be observed clearly in Panel (d), in which both the optimized percentage of debt and the relative mix of senior and junior debt are shown at different levels of portfolio size.

Finally, we consider the case where our clinical success rates are systematically off by a relative factor (from -10% to +10%) for each phase (yielding a compounded factor through multiple phases). We compare a fixed structure RBO (solid blue line) to the all-equity structure (dotted black line) in Figure A-3. In particular, we observe in panel b) that for a -10% factor at each phase, the senior default probability nearly
Figure A-3: Comparison of fixed capital structure RBO structure (solid blue line) with an all-equity structure (dotted black-line) where the clinical probabilities of success shown in Table 3.1 are scaled by a relative variable amount. A capital of $575 is used to purchase 8 pre-clinical and 8 phase 1 compounds. The RBO structure uses $86.25 million senior tranche and $115 million junior tranche. Compounds are intended to be sold upon completion of Phase 2 trials.

doubles but is still fairly conservative at 2bp. Similarly, in panel c) we see that the default probability on the junior tranche increases to about 1.1%. Panel a) shows that for the a factor of -10% at each phase, the average return on equity falls below that of the all-equity structure due to the fixed promised coupon rates to the debt holders. Finally in panel d) we see that the probability of equity loss increases for both structures by about a factor of 2.

A.2 Orphan Simulation Validation

In this section we demonstrate our approach of simulation validation through unit testing and external validation. In particular we provide one example of the up-
Table A.1: Results using the parameters from Table 3.3 (third column), but with infinite cash (first column) so that trials are always immediately funded, and deterministic trials (second column) so that trials always complete within the simulation horizon.

Dated orphan results from the second column of Table 3.3 using log-normal clinical trial times. Table A.1 compares the average number of compounds reaching specific phases of development when the fund is guaranteed to fund trials immediately (unlimited cash), and when the trial duration is deterministic and therefore guaranteed to complete within the fixed simulation horizon. We can estimate these numbers externally using the probabilities of success and distributions of clinical trial timing. For example, the number to reach $P3$ should be the number of Pre-Clinical projects acquired multiplied by the probabilities of success at each phase $8(.69)(.84)(.53) = 2.46$ plus the analogous calculation for Phase 1 projects, $8(.84)(.53) = 3.56$ for a total of 6.0 compounds reaching Phase 3 in agreement with the simulation framework under unlimited cash and deterministic timing. Under uncertain (log-normal) clinical trial times, the calculation is additionally multiplied by the probability of projects reaching $P3$ within the simulation horizon (6 years of potential development time), which approximates to 72.5% for compounds starting from Pre-Clinical stage and 84% from Phase 1, resulting in 1.78 and 2.99 compounds, respectively, for a total average of 4.77 compounds reaching Phase 3 - in agreement with the simulation results. Similarly, approximately 5.5% and 3.0% of compounds will remain in Phase 1 when starting in Pre-clinical or Phase 1 respectively, resulting in $8(.69)(.055)+8(.03) = 0.54$ compounds remaining in Phase 1, quite close to the simulation with unlimited cash. Ultimately, for the standard case of limited capital, the number of compounds reaching Phase 3 is further reduced because funds may not be available immediately.

Table A.2 has raw and annualized return on equity values. Based on the number of compounds in the previous step, we can estimate the raw ROE using the assumptions.
Table A.2: Results using the parameters from Table 3.3 (second column), but with deterministic valuations (first column) to isolate Jensen’s inequality type effects.

of average valuations by phase. In particular, we can use the following approximate formula,

$$\text{ROE} \approx fV_{P3}n_{P3} + fV_{P2}n_{P2} + fV_{P1}n_{P1} + S - P - I - C,$$

(A.1)

where $f$ is the equity stake, $V_{P1-3}$ is the mean value of Phase 1-3 assets, $n_{P1-3}$ is the average number of assets remaining or sold in that phase at horizon, $S$ is the total capital, $P + I$ is the total principal and interest, and $C$ is the average amount spent on costs for all the assets. Using the numbers from Table A.2 for number of assets reaching specific phases, Equation A.1 yields (with 85% equity stake), $321.5(.85)(4.3)+75.6(.85)(2.7)+27.6(.85)(0.56)+575-275-500)/373.75-1 = 2.11$, close to that obtained through simulation. Note that $C$ is estimated from the simulation itself. For the annualized ROE, this yields 16.3% which is slightly higher than the simulation average due to Jensen’s inequality from uncertainty in the number of successes. The effect due to Jensen’s from annualizing is even more significant in the presence of valuation uncertainty as well, reducing to 12.9% with similar compound throughput. Further validation could be done in a similar manner for higher moments or other summary statistics, using this type of unit testing approach.
Appendix B

NCATS Supplementary Materials\textsuperscript{1}

B.1 Simulation Calibration

We first aggregate observations by stage, including IND-Enabling, IND-Filing, Phase 1 and Phase 2. Using these observations, we calculate the averages and standard deviations of both the stage duration and cost as shown in Table B.1. To expand our sample size of clinical outcomes, we include trials that were completed by collaborators upon exiting the BrIDGs program. Finally, we include costs borne by NCATS as well as its collaborators.

A first step is to combine the IND-Enabling and Filing stages into a single pre-

\textsuperscript{1}This appendix was published as the supplementary materials of Fagnan et al. (2015)[23]

<table>
<thead>
<tr>
<th>Observation</th>
<th>IND-Enabling</th>
<th>IND-Filing</th>
<th>Phase 1</th>
<th>Phase 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Num. of NCATS Trials</td>
<td>10</td>
<td>4</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Num. of Collaborator Trials</td>
<td>0</td>
<td>0</td>
<td>5</td>
<td>3</td>
</tr>
<tr>
<td>NCATS &amp; Collaborator Success</td>
<td>90%</td>
<td>100%</td>
<td>100%</td>
<td>75%</td>
</tr>
<tr>
<td>Average NCATS Durations (months)</td>
<td>26.9</td>
<td>3</td>
<td>11</td>
<td>6</td>
</tr>
<tr>
<td>Std. Dev. NCATS Duration (months)</td>
<td>12.54</td>
<td>0</td>
<td>5.66</td>
<td>NA</td>
</tr>
<tr>
<td>Average NCATS Cost ($ millions)</td>
<td>1.84</td>
<td>0.714</td>
<td>1.07</td>
<td>0.824</td>
</tr>
<tr>
<td>Std. Dev. NCATS Cost ($ millions)</td>
<td>2.02</td>
<td>0.159</td>
<td>0.800</td>
<td>NA</td>
</tr>
</tbody>
</table>

Table B.1: Observations of NCATS rare-disease projects including success, duration, and cost of trials. In addition success rates include trials completed by collaborators after completing the BrIDGs program. Projects included are those that have undergone a change in status since becoming active, particularly the first round of TRND and BrIDGs rare-disease projects.
Table B.2: Prior weight given to literature data for orphan diseases [22], with lower values relying more on the NCATS observations. Larger weights are used for later stages, where there are fewer observations.

Table B.3: Posterior estimates of parameters for simulating an NCATS rare-disease megafund, combining literature estimates for orphan diseases [22].

clinical stage, which is done by adding the costs and durations. Finally, we combine the NCATS observations with previous literature estimates for orphan disease by choosing linear prior weights presented in Table B.2. Higher prior weights are used on clinical trials where there are fewer NCATS observations, while lower prior weights are used in the pre-clinical stage. Due to the NCATS business model, we expect the pre-clinical stage to take significantly longer but to cost less than literature estimates, resulting in lower prior weights on these parameters.

Finally, by applying these prior weights, we arrive at the posterior estimates shown in Table B.3 which are then used as inputs to the simulation framework as discussed in Section B.3. Note that there were no estimates of standard deviation for duration in previous work, as a geometric distribution was used, so we use a fixed ratio for all stages. The calibration of the valuation parameters is discussed in Section B.2.

### B.2 Valuation Panel and Calibration

A list of key comments from panel respondents are summarized in Table B.4. In addition to collecting raw valuations, we calculate panel aggregates to use in the calibration of simulation inputs. We focus on the panel median of the best guess
Key Comment Summary

- In real life we spend weeks with a team to evaluate a single project, including IP review. Overall this is a very quick read based on limited information.
- Fairly arbitrary.
- The markets are proving so receptive right now that it felt most appropriate to link valuation estimates to recent deals (2012 & 2013)
- Focused on value for US markets, using a fixed risk of failure for each milestone. I did not account for disease circumstances beyond the number of potential patients, and the current pipeline position of the project.

Table B.4: Summary of key comments from valuation panel respondents when asked to value a portfolio of rare-disease projects within NCATS.

<table>
<thead>
<tr>
<th>Valuation Estimate or Choice</th>
<th>Pre-clinical</th>
<th>Phase 1</th>
<th>Phase 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Panel Median Valuation ($ millions)</td>
<td>8.22</td>
<td>20.8</td>
<td>40.0</td>
</tr>
<tr>
<td>Fagnan et al. Valuation ($ millions)</td>
<td>7.1</td>
<td>27.6</td>
<td>75.6</td>
</tr>
<tr>
<td>Valuation Prior Weight</td>
<td>50.0%</td>
<td>50.0%</td>
<td>50.0%</td>
</tr>
<tr>
<td>Average Valuation Posterior</td>
<td>7.66</td>
<td>24.20</td>
<td>57.8</td>
</tr>
</tbody>
</table>

Table B.5: Panel median valuations compared with literature estimates for orphan diseases [22]. Posterior estimates used in simulation are taken to be equally weighted between the panel and literature estimates.

of respondents to reduce the impact of outliers, and weight it equally with existing literature estimates. Given the lack of projects valued at the completion of Phase 2, we rely solely on previous literature estimates for the valuation of later-stage compounds. The resulting posterior estimates of valuations are presented in Table B.5.

B.3 Simulation Framework

Our simulation framework assumes capital is acquired on day one, which is used to acquire $n$ projects during the first 6 months. Although the simulation framework can acquire projects at any stage, the examples in this study acquire either 9 or 16
Table B.6: Parameters and distributions used in simulation framework for an NCATS rare-disease megafund. Missing entries are not used in this set of simulations, which carries projects only to completion of Phase 2.

Pre-clinical compounds depending on the structure. Compounds in a given stage are assumed to have success drawn from independent and identically distributed (IID) Bernoulli random variables, with trial duration drawn from IID log-normal random variables. Parameters for success and duration are presented in Table B.6. Projects are intended to be carried to a pre-determined target stage that, in this study, is chosen to be Phase 3. The process of selling a project is assumed to take one year.

A portion (85%) of the equity is acquired for an upfront payment of a fixed amount for a given stage with the promise of potential future milestone payments. The upfront values presented in Table B.6 are determined by discounting the average valuation of the current stage by the equity fraction, and subtracting the costs for current-stage costs. In addition, the original equity holder receives milestone payments (see Table B.6) for each successfully completed clinical trial. We also prevent the situation of selling compounds that have not transitioned from their current stage.

In contrast to previous work, we assume that clinical trial times are log-normally distributed, a more realistic choice than geometric as used in Fagnan et al. (2014). For the pre-clinical stage, we fit a log-normal distribution to the first and second moments of the observed clinical trial times. For later stages, we assume a log-normal distribution using a standard deviation to mean ratio of 0.5, close to the
value observed for pre-clinical data. We ignore the possibility of stages being skipped or not needed, which is occasionally observed with certain rare diseases or re-purposed drugs.

Using discrete 6-month time steps, our simulation framework checks for progress from any of the current clinical trials. Once a trial is completed, it is either advanced or withdrawn according to a random Bernoulli draw. For the project to continue, debt and interest coverage obligations must be satisfied before the next trial can be funded with any remaining cash. If debt and interest coverage obligations cannot be met, compounds are sold prior to the target-stage to cover the shortfall.

Clinical costs and project valuations are assumed to be distributed according to a capped log-normal distribution. We use the same standard deviation and maximum of valuations employed by Fagnan et al. (2014). Upon the sale of a compound, the valuation is drawn from a log-normal distribution with correlation $\rho$ to a single underlying market factor of 20%.

## B.4 Sensitivity Analysis

To provide further insight into the details of the simulation results, we provide a number of sensitivity analyses for the RBO structure presented in Table 5.2.

### B.4.1 Clinical-Time Distribution

We compare results for the RBO structure in Table 5.2 for four additional clinical trial time distributions, including geometric (used in previous works), log-normal, truncated normal and uniform. We calibrate each distribution to our estimates of mean and variance of clinical trial times, except for geometric which is fit using only the mean. We provide plots of the density functions in Figure B-1 and similar calibrations are performed at each stage of the drug development process. Note that due to the discrete time simulation framework, trials are only checked for completion every 6 months, and thus cannot finish in less than 6 months.

For each distribution, Table B.7 compares several performance metrics using the
Figure B-1: Plot of density functions for various Phase 2 clinical trial time distributions calibrated by matching first and second moments. The black line shows the mean of all distributions.

same simulation setup with fixed RBO structure as in the main paper with 200,000 simulations for each clinical trial time distribution. The geometric distribution is the most different, allowing about an extra 0.4 compounds on average to reach Phase 3, and a 7% increase in MIRR due to the higher chance of quick clinical trials. Coupled with this is increased default rates on the bonds, as money is spent faster on trials, the risk is greater when trials fail and there are fewer compounds to liquidate for interest coverage. The other three distributions are quite similar across all metrics, with the LogNormal having the lowest average compounds reaching Phase 3 due to the higher chance of long clinical trial times.

B.4.2 Valuation Distribution

We compare results for the RBO structure in Table 5.2 for four additional valuation distributions, including a truncated normal distribution, Weibull, Pareto, and gamma. We calibrate each distribution to our estimates of the mean and variance of valuations. The correlation is performed in normal space, before mapping to Uniform and then inverting to the desired distribution, as is done for the main paper. Although this
Table B.7: Performance metrics for RBO structure (without guarantee) from Table 5.2 for alternative clinical trial time distributions.

<table>
<thead>
<tr>
<th>Distribution</th>
<th>Performance Metric</th>
<th>LogNormal</th>
<th>Uniform</th>
<th>Geometric</th>
<th>Truncated Normal (0,inf)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Phase 2 Sold</td>
<td>1.9</td>
<td>1.2</td>
<td>1.8</td>
<td>1.8</td>
<td>1.8</td>
</tr>
<tr>
<td>Phase 3 Sold</td>
<td>5.3</td>
<td>5.7</td>
<td>5.44</td>
<td>5.5</td>
<td></td>
</tr>
<tr>
<td>Raw ROE</td>
<td>5.1</td>
<td>5.2</td>
<td>5.2</td>
<td>5.2</td>
<td></td>
</tr>
<tr>
<td>Annualized ROE</td>
<td>14.7%</td>
<td>14.3%</td>
<td>14.8%</td>
<td>14.8%</td>
<td></td>
</tr>
<tr>
<td>MIRR</td>
<td>21.6%</td>
<td>28.5%</td>
<td>21.5%</td>
<td>21.6%</td>
<td></td>
</tr>
<tr>
<td>Pr(loss of equity)</td>
<td>6.2%</td>
<td>6.3%</td>
<td>6.2%</td>
<td>6.4%</td>
<td></td>
</tr>
<tr>
<td>Pr(ROE &gt; 25%)</td>
<td>10.4%</td>
<td>10.8%</td>
<td>10.9%</td>
<td>11.1%</td>
<td></td>
</tr>
<tr>
<td>Pr(Senior Default)</td>
<td>0.1 bp</td>
<td>1.5 bp</td>
<td>0.1 bp</td>
<td>0.1 bp</td>
<td></td>
</tr>
<tr>
<td>Pr(Junior Default)</td>
<td>47 bp</td>
<td>99 bp</td>
<td>48 bp</td>
<td>51 bp</td>
<td></td>
</tr>
</tbody>
</table>

Table B.8: Calibrated parameters for valuation distributions at Phase 3.

<table>
<thead>
<tr>
<th>Distribution</th>
<th>Parameter</th>
<th>LogNormal w/ Cap</th>
<th>Truncated Normal</th>
<th>Weibull</th>
<th>Gamma</th>
<th>Pareto</th>
</tr>
</thead>
<tbody>
<tr>
<td>μ</td>
<td>5.44</td>
<td>185.6</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>σ</td>
<td>0.939</td>
<td>301.3</td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>shape</td>
<td></td>
<td>1.20</td>
<td>1.45</td>
<td>2.56</td>
<td></td>
<td></td>
</tr>
<tr>
<td>scale</td>
<td></td>
<td>341.6</td>
<td>222.3</td>
<td>195.7</td>
<td></td>
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<tr>
<td>cap</td>
<td></td>
<td>1000</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

The calibrated parameters for Phase 3 are provided in Table B.8. We also provide plots of the density functions in Figure B-2. For each case, the distribution is also calibrated at other stages of the drug-development process for the event of early sales.

For each distribution, Table B.9 compares several performance metrics using the same simulation setup with fixed RBO structure as in the main paper with 200,000 simulations for each distribution. The MIRR varies only by 0.2%, while the annualized ROE varies by slightly more than 1% across distributions. The Pareto distribution has the least risk to the bonds, as expected since it has a minimum value above zero. The default risk to the bonds is highest for the Weibull, which stays within reasonable limits at 62 bp for the junior and less than 1 for the senior tranche. The average number of compounds carried to Phase 3 is the same for all distributions at 5.3.
Figure B-2: Plot of density functions for various Phase 3 valuation distributions calibrated using first and second moment matching. The black line shows the mean of all distributions.

<table>
<thead>
<tr>
<th>Performance Metric</th>
<th>Distribution</th>
<th>Bounded Log-Normal</th>
<th>Truncated Normal</th>
<th>Weibull</th>
<th>Gamma</th>
<th>Pareto</th>
</tr>
</thead>
<tbody>
<tr>
<td>Phase 2 Sold</td>
<td></td>
<td>1.9</td>
<td>2.0</td>
<td>2.0</td>
<td>2.0</td>
<td>2.0</td>
</tr>
<tr>
<td>Phase 3 Sold</td>
<td></td>
<td>5.3</td>
<td>5.3</td>
<td>5.3</td>
<td>5.3</td>
<td>5.3</td>
</tr>
<tr>
<td>Raw ROE</td>
<td></td>
<td>5.1</td>
<td>5.1</td>
<td>5.1</td>
<td>5.1</td>
<td>5.0</td>
</tr>
<tr>
<td>Annualized ROE</td>
<td></td>
<td>14.7%</td>
<td>15.1%</td>
<td>14.5%</td>
<td>14.6%</td>
<td>15.8%</td>
</tr>
<tr>
<td>MIRR</td>
<td></td>
<td>21.6%</td>
<td>21.7%</td>
<td>21.5%</td>
<td>21.6%</td>
<td>21.8%</td>
</tr>
<tr>
<td>Pr(loss of equity)</td>
<td></td>
<td>6.2%</td>
<td>5.5%</td>
<td>6.7%</td>
<td>6.4%</td>
<td>3.5%</td>
</tr>
<tr>
<td>Pr(ROE &gt; 25%)</td>
<td></td>
<td>10.4%</td>
<td>7.9%</td>
<td>10.2%</td>
<td>10.1%</td>
<td>6.0%</td>
</tr>
<tr>
<td>Pr(Senior Default (b.p.))</td>
<td></td>
<td>0.1</td>
<td>0.3</td>
<td>0.4</td>
<td>0.2</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Pr(Junior Default (b.p.))</td>
<td></td>
<td>47</td>
<td>42</td>
<td>62</td>
<td>56</td>
<td>1</td>
</tr>
</tbody>
</table>

Table B.9: Performance metrics for RBO structure (without guarantee) from Table 5.2 for alternative valuation distributions.
B.4.3 Probability of Success

We show how annualized ROE, MIRR, risk of equity loss, and chance of annualized ROE over 25% depend on the probability of success. As shown in Figure B-3, each metric is quite linear since the total value scales with the expected number of success which is linear in probability of total success $p$. Table B.10 shows additional metrics, including the risk to the bonds which increases only slightly for the junior tranche at -15% relative adjustment.

B.4.4 Valuation

We show how annualized ROE, MIRR, risk of equity loss, and chance of annualized ROE over 25% depend on the Phase 3 valuation. Figure B-4 shows the performance of four metrics, for adjusted mean and standard deviation of Phase 3 valuations. ROE and MIRR appear quite linear, with less sensitivity to the valuation as to the probability of success. Table B.11 shows additional metrics, including the risk to the bonds which increases by only 7bp at -15% relative adjustment.
### Table B.10: Performance metrics for RBO structure (without guarantee) from Table 5.2 for adjusted probability of success applied to all stages.

<table>
<thead>
<tr>
<th>Performance Metric</th>
<th>-15%</th>
<th>-10%</th>
<th>-5%</th>
<th>0%</th>
<th>+5%</th>
<th>+10%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Phase 2 Sold</td>
<td>2.1</td>
<td>2.0</td>
<td>2.0</td>
<td>1.9</td>
<td>1.6</td>
<td>1.3</td>
</tr>
<tr>
<td>Phase 3 Sold</td>
<td>5.2</td>
<td>5.3</td>
<td>5.3</td>
<td>5.3</td>
<td>5.2</td>
<td>5.0</td>
</tr>
<tr>
<td>Raw ROE</td>
<td>3.3</td>
<td>3.9</td>
<td>4.5</td>
<td>5.1</td>
<td>5.7</td>
<td>6.1</td>
</tr>
<tr>
<td>Annualized ROE</td>
<td>10.6%</td>
<td>12.1%</td>
<td>13.4%</td>
<td>14.7%</td>
<td>16.2%</td>
<td>17.2%</td>
</tr>
<tr>
<td>MIRR</td>
<td>15.8%</td>
<td>17.8%</td>
<td>19.7%</td>
<td>21.6%</td>
<td>23.7%</td>
<td>25.6%</td>
</tr>
<tr>
<td>Pr(loss of equity)</td>
<td>10.8%</td>
<td>8.8%</td>
<td>7.3%</td>
<td>6.2%</td>
<td>4.3%</td>
<td>3.1%</td>
</tr>
<tr>
<td>Pr(ROE &gt; 25%)</td>
<td>3.3%</td>
<td>5.1%</td>
<td>7.4%</td>
<td>10.4%</td>
<td>12.7%</td>
<td>14.8%</td>
</tr>
<tr>
<td>Pr(Senior Default)</td>
<td>&lt;0.1 bp</td>
<td>0.1 bp</td>
<td>&lt;0.1 bp</td>
<td>0.1 bp</td>
<td>&lt;0.1 bp</td>
<td>&lt;0.1 bp</td>
</tr>
<tr>
<td>Pr(Junior Default)</td>
<td>65 bp</td>
<td>57 bp</td>
<td>53 bp</td>
<td>47 bp</td>
<td>19 bp</td>
<td>5.5 bp</td>
</tr>
</tbody>
</table>

Figure B-4: Performance metrics for RBO structure (without guarantee) from Table 5.2 for adjusted mean and standard deviation of Phase 3 valuation.
## B.5 Measures of Financial Performance

We provide several measures of the performance of a given structure of equity. For a single simulation path, the cash at the end of period \( t \) is \( c_t \), and the net cash flows in a given period are \( f_t \),

\[
f_t = c_t - c_{t-1}
\]  
(B.1)

where \( t \) runs from period 0 through the simulation horizon \( T \).

The standard measure reported in previous works has been the average annualized return on equity (ROE) relative to the initial equity investment \( e \),

\[
\text{ROE} = E \left[ \left( \frac{c_T}{e} \right)^{2/T} - 1 \right],
\]  
(B.2)

where \( T \) is the simulation horizon, the number of semi-annual periods. Although reasonable, this measure does not convey the likelihood of cash flows significantly earlier than the simulation horizon due to variance in clinical trial times or starting project stage.

To capture the prospect of earlier cash flows, we provide additional measures of performance. Typically, the venture capital community reports internal rates of return (IRR), which assumes the same discount rate for all net cash flows (positive
or negative). The IRR is the solution to the following equation:

\[
\sum_{t=0}^{T} \frac{f_t}{(1 + \text{IRR})^t} = 0.
\]  

(B.3)

Unfortunately, in the presence of alternating cash flows, the IRR is not unique. One simple example is the consecutive cash flows \((-10, 21, -11)\) which yields an IRR of 0% and 10%.

As a result, we introduce an additional metric, known as the modified internal rate of return (MIRR). This is a generalization of IRR that requires two parameters, the finance rate \((r_{fi})\) and reinvestment rate \((r_{re})\) which discount negative and positive cash flows, respectively. We include one choice of MIRR, denoted MIRR\(_0\) where we set the finance rate \(r_{fi} = 0\), and the reinvestment rate equal to the MIRR \(r_{re} = \text{MIRR}_0\). Hence, the solution for a given sample path is given by,

\[
\sum_{t=0}^{T} f_t^- + \frac{f_t^+}{(1 + \text{MIRR}_0)^t} = 0
\]  

(B.4)

where \(f_t^- \equiv \min(f_t, 0)\) are the negative cash flows and \(f_t^+ \equiv \max(f_t, 0)\) are the positive cash flows. The MIRR provides a reasonable measure that rewards earlier cash flows by applying the reinvestment rate. Finally, for comparison to quoted venture capital IRR rates, we solve (B.3) using MIRR\(_0\) as a starting point and include this for the all-equity structure.

Lastly, we also include the average raw return on equity, ROE\(_{\text{raw}}\), which is not annualized

\[
\text{ROE}_{\text{raw}} = \mathbb{E} \left[ \left( \frac{C_T}{e} \right) - 1 \right].
\]  

(B.5)

Although this metric may seem simplistic, it is clear and intuitive.
Bibliography


