Financing Correlated Drug Development Projects

Andrew W. Lo and Kien Wei Siah

Andrew W. Lo
is the Charles E. and Susan T. Harris Professor at the MIT Sloan School of Management, director of the MIT Laboratory for Financial Engineering, a principal investigator at the MIT Computer Science and Artificial Intelligence Laboratory, and an affiliated faculty member of the MIT Department of Electrical Engineering and Computer Science in Cambridge, MA, and an external faculty member at the Santa Fe Institute in Santa Fe, NM.
alo-admin@mit.edu

Kien Wei Siah
is a PhD candidate in the MIT Department of Electrical Engineering and Computer Science in Cambridge, MA.
kienwei@mit.edu

KEY FINDINGS

- The performance of a biomedical megafund becomes less attractive when correlation between phase transitions in drug development projects is introduced.
- The risk of default and the expected returns of the vanilla megafund remain promising to fixed-income investors and equity holders, even under moderate levels of correlation.
- A leveraged megafund outperforms an equity-only structure over a wide range of assumptions about correlation and probability of success.

ABSTRACT

Current business models have struggled to support early-stage drug development. In this paper, we study an alternative financing model, the megafund structure, to fund drug discovery. We extend the framework proposed in previous studies to account for correlation between phase transitions in drug development projects, thus making the model a more realistic representation of biopharma research and development. In addition, we update the parameters used in our simulation with more recent estimates of the probability of success (PoS). We find that the performance of the megafund becomes less attractive when correlation between projects is introduced. However, the risk of default and the expected returns of the vanilla megafund remain promising even under moderate levels of correlation. In addition, we find that a leveraged megafund outperforms an equity-only structure over a wide range of assumptions about correlation and PoS.

TOPICS

Portfolio theory, portfolio construction, equity portfolio management, asset-backed securities (ABS), mutual funds/passive investing/indexing, simulations, performance measurement*

The drug development process has become increasingly expensive and risky over the past few decades. This phenomenon can be attributed to the rising cost of clinical trials and a shift in research focus to more complex biological mechanisms that are potentially more transformative but also have higher risks of failure. As a result, the current business model for research and development (R&D) in biopharma is becoming less effective. This is reflected in the decline of R&D productivity and the lackluster performance of investments in the biotech and pharma sectors in recent years.

Fernandez, Stein, and Lo (2012) proposed a megafund structure to address this issue. This structure pools a large number of biomedical programs together in its portfolio, thus diversifying the risk of drug development and increasing the likelihood

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of success through multiple "shots on goal." By tranching this structure and redistributing the risk of default, the megafund can tap into the fixed income market, a substantially larger pool of capital than the conventional sources of biopharma R&D financing—public and private equity—but one traditionally unwilling to participate in biopharma investments due to the risky and fragmented nature of drug development. The megafund finances its large portfolio using capital raised from issuing equity and debt, that is, bonds collateralized by the portfolio of pipeline drugs and their associated intellectual property. Simulation results by Fernandez, Stein, and Lo (2012) show that this alternative financial structure can yield reasonable returns for investors in both types of securities.

More recently, Fagnan et al. (2014, 2015) applied the megafund approach to early-stage drug development—the riskiest part of the drug discovery process and the one where funding is also the scarcest. They found that the megafund structure is particularly well suited for financing orphan drugs, which typically have higher probabilities of success, lower clinical costs, and shorter development times than their non-orphan counterparts. In their simulations, an orphan drug megafund managed to generate double-digit annualized returns with a portfolio of only 10 to 20 orphan drug projects.

In this paper, we use the multi-state, multi-period simulation framework described in Fernandez, Stein, and Lo (2012) and Fagnan et al. (2014, 2015) to analyze the potential performance of an orphan drug megafund. However, we note that the assumption of independent phase transitions of previous megafund studies rarely holds in practice, since drug candidates tend to exhibit some amount of correlation with one another, depending on the similarities of their underlying treatment pathways. We demonstrate that the presence of correlated transitions has important consequences for the performance of the megafund, as seen in our formal derivation and empirical results (Online Supplement B and Results, respectively). To obtain a more realistic representation of biopharma R&D, we examined the use of a single-factor model with a Gaussian copula to model correlations among pipeline drugs in the portfolio. This approach allows us to evaluate the tail risks of the megafund more accurately.

In addition, we update the parameters for clinical trial durations and probabilities of success based on the estimates reported by Wong, Siah, and Lo (2019) in a recent study. We also simulate the performance of several different megafund structures with correlated portfolios (vanilla, guarantee-backed, and equity-only), and perform a sensitivity analysis of several key parameters in our framework, specifically the capital structure, the portfolio acquisition strategy, the level of correlation among projects, and the probabilities of success for phase transitions.

Along with our results, we release an open-source version of our simulation software, and encourage readers to rerun our simulations with their own preferred set of assumptions and inputs.

METHODS

Framework

A drug development megafund is a financial entity that pools and repackages a portfolio of pipeline drug assets into an arbitrary number of tranches with different risk, reward, and maturity characteristics. It offers the repackaged securities to investors as "research-backed obligations" (RBOs)—that is, debt and equity securities backed by the pool of underlying drug assets—and uses the capital raised to finance the development of pipeline drugs in its portfolio. The RBO is structured to follow a strict priority for cash flow distributions. In general, senior debt tranches have first priority on the cash flows generated by the portfolio, and therefore have the best credit rating. Mezzanine tranches have the second claim on cash flows, but they are

compensated by higher coupon rates for the higher risk of default. Finally, equity holders bear the risk of first loss, but at the same time, they are entitled to all the residual cash from debt repayment.

In this paper, we consider an RBO structure with the same three types of tranches: senior debt, junior debt, and equity. In addition to the subordination of cash flows, however, we adopt credit enhancement mechanisms designed to provide additional protection for the bondholders (Hull, Lo, and Stein 2019): we maintain a reserve account at levels in excess of the fund's current liabilities, that is, its short-term interest and principal payments. This account is tracked periodically to ensure that it remains above a minimum target level, failing which assets are liquidated to cover the shortfall. These coverage triggers can prevent the fund from abruptly going into default by identifying potential shortfalls ahead of time, thus giving portfolio managers sufficient lead time to monetize available assets. This is especially important for assets that are relatively illiquid, such as drug development programs, where extensive negotiation is necessary and there is a lag between the sale of a project and the actual cash inflow.

We assume an investment structure based on the licensing framework commonly used in the biopharmaceutical industry (Fernandez, Stein, and Lo 2012). The megafund first acquires a majority stake in each drug development program for an upfront payment. In our model, pipeline drugs undergo the standard drug approval process: starting from pre-clinical research and advancing through phase 1, phase 2, phase 3, and New Drug Application (NDA), before finally gaining approval. Each stage of development requires a certain amount of time and funding, at the end of which the program will either progress to the next higher phase or be discontinued. In exchange for the majority stake, the megafund is responsible for all clinical trial expenses ("development costs"), and also any milestone payments due to the project investigators for the successful completion of each phase of development. Pipeline drugs are typically financed up to a specific target phase before being monetized, but they also can be sold for revenue at any point during development. As mentioned earlier, we assume that there is some lag time between a sale and the actual cash inflow.

The cash flow waterfall of the megafund is complex. In addition to periodic debt and interest payments, investments in pipeline drugs at each phase of development must be carefully managed to ensure that the interest coverage ratio remains above a minimum level. Depending on the performance of the portfolio, projects may need to be either put on hold until sufficient capital becomes available, or prematurely liquidated prior to the target phase, to make up for any shortfall in cash flows.

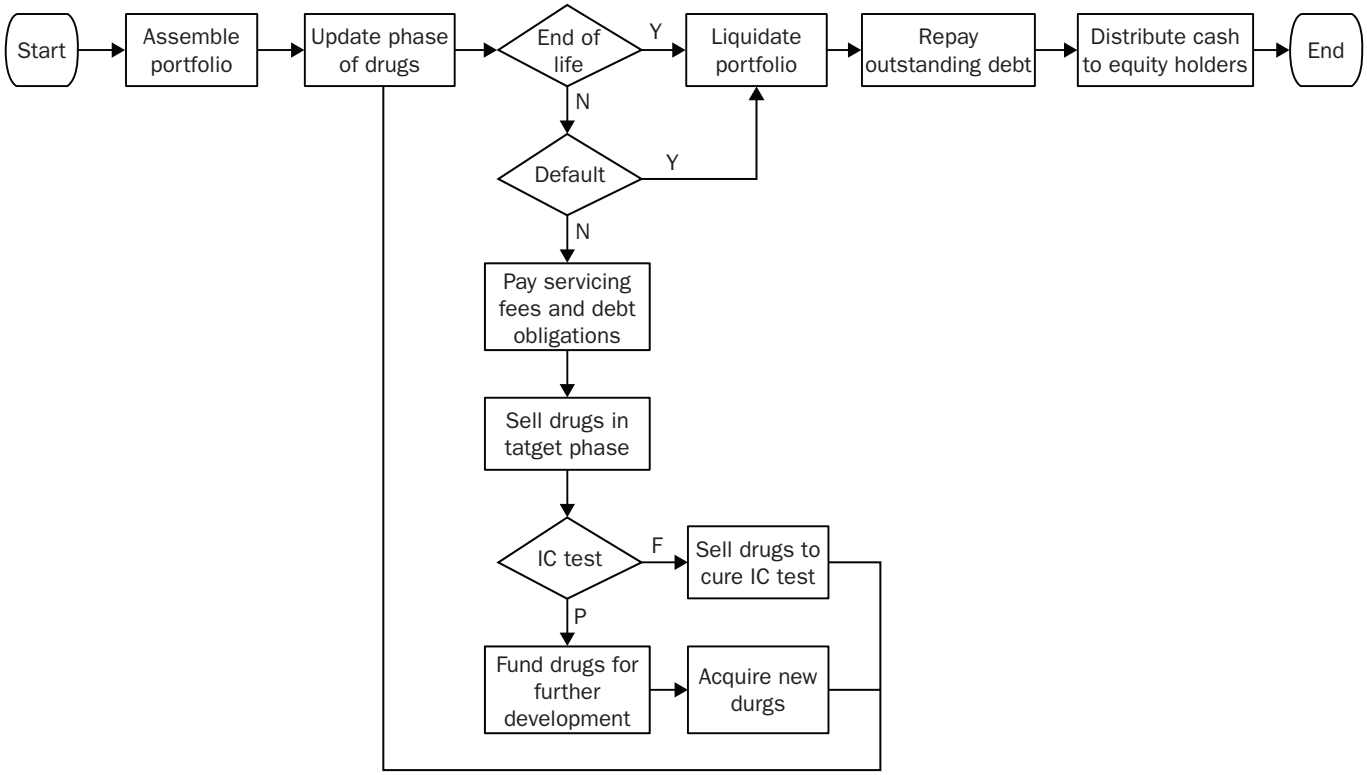
We use a multi-period Monte Carlo simulation model to evaluate the returns of the megafund over a fixed time horizon (see Exhibit 1). We assume that the fund assembles a portfolio of drug development programs at the start of the simulation. We compute the financial statistics of the fund and the performance of the portfolio at discretized time steps ("periods") and allocate the cash flows in each period according to the waterfall structure. We assume that the phase transitions follow a stochastic process, with the clinical trial cost, testing duration, and asset valuation drawn from continuous random distributions. When the end of life of the fund is reached, or if the fund defaults on its bond payments at any point during its tenor, the portfolio is liquidated. The proceeds are used to repay all outstanding debt, and any residual cash is distributed to the equity holders. Thereafter, the megafund is dissolved.

Parameters

In our simulation, we assume that the megafund has a tenor of 10 years and a capital structure comprising three tranches: a senior debt tranche, a junior debt tranche, and an equity tranche. At the start of each simulation, the fund raises $575 million of capital, including $250 million from senior debt, $50 million from

EXHIBIT 1

Simulation Framework for the Megafund



NOTES: The cash flow waterfall incorporates the subordination of cash flow, the credit enhancement mechanism, the investment structure of drug development, and the drug approval process. Pipeline drugs that successfully advance to the next phase are funded only if there is sufficient cash remaining after settling current liabilities and fulfilling the interest coverage test. If not, they are held in the portfolio without further development until additional capital becomes available. The sale of pipeline drugs is the dominant source of cash flow for the megafund.

ABBREVIATIONS: Y, yes; N, no; F, fail; P, pass; IC, interest coverage.

junior debt, and $275 million from equity. The senior bonds are structured to have a maturity of five years with an annual coupon rate of 5%, and the junior bonds nine years with 8%. Each tranche is amortized evenly (i.e., straight-line amortization) over the four-year interval preceding its date of maturity. The schedule is structured so that principal payments do not overlap, and junior bonds are retired only after senior bonds have been fully redeemed.

We discretize the simulation horizon into six-month time periods, and assume that the megafund makes debt and coupon payments at the end of each period (i.e., semiannual payouts) according to the amortization schedules of the bonds. In addition, we assume that the sale of each drug development program takes a year to settle, from the initiation of transaction to the receipt of cash proceeds. Therefore, we consider a simulation horizon of 10 years, which spans the tenor of the fund, and leaves an additional year at the end for portfolio liquidation. In the absence of default, all clinical assets that have not already been sold or discontinued at the end of the ninth year are liquidated, and the proceeds received in the last period are distributed to the equity investors.

In this paper, we focus on early-stage orphan drug development projects for the RBO portfolio. We assume that the megafund acquires 23 pre-clinical programs at the start of simulation, with the aim of funding them through the completion of phase

2 clinical testing (i.e., to phase 3) before their sale. This is the maximum number of drugs the megafund can afford to finance, based on the amount of capital raised and the expected development cost required for each drug to reach the target phase. Each acquisition grants the megafund an 85% ownership stake in the asset, thus entitling the fund to the same portion of proceeds when the asset is monetized.

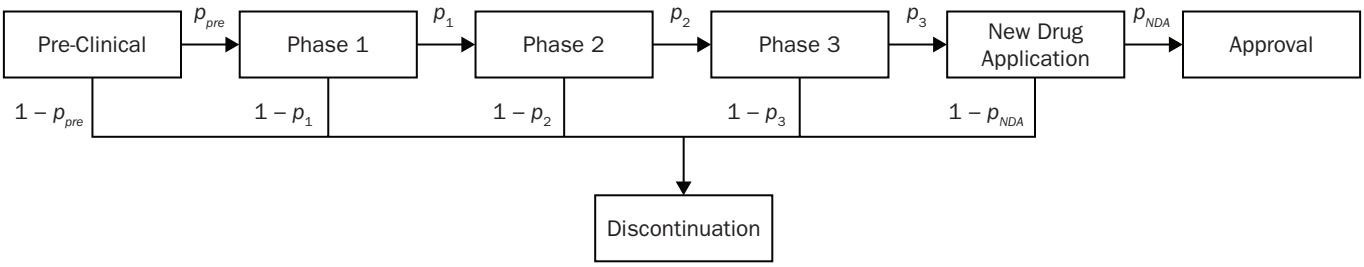
The simulation framework relies on several important modeling assumptions regarding the cost of clinical trials, the duration of clinical testing, asset valuation, and phase transition. Following the approach by Fagnan et al. (2015), we model the cost and duration of clinical trials at each phase of development as independent and identically distributed (IID) log-normal random variables. We impose an upper bound on the development cost of each phase to limit the maximum possible expense that can be incurred per compound. Upfront costs and milestone payments are taken to be constants based on the phase of development. Similar to our treatment of development costs, we assume an upper-bounded log-normal distribution for drug asset valuation at each stage of development. However, instead of imposing independence, we introduce pairwise correlation of market valuation between projects using a single-factor model (see Online Supplement A).

We model the drug development process as a sequence of Bernoulli trials, that is, as a Bernoulli process: at each phase of development k, a pipeline drug has some probability p_k of advancing to the next higher phase $k + 1$ ("success") and probability $1 - p_k$ of being discontinued ("failure"). The time spent in each phase depends on the clinical testing duration drawn from the log-normal distribution described earlier. In our model, discontinuation is assumed to be an absorbing state, that is, a drug that has been withdrawn can no longer reenter the development process (see Exhibit 2).

Fagnan et al. (2015) modeled phase transitions as IID random variables. However, we note that the assumption of independence rarely holds in practice, since drugs tend to exhibit some amount of correlation with one another, depending on the similarities in their underlying scientific pathways, mechanisms, and targets (e.g., two drugs with similar mechanisms of action are likely to have similar outcomes in testing). The presence of correlation has significant implications for the performance of the megafund. In general, correlation among assets introduces systematic risk to the portfolio that, by definition, cannot be diversified away. Increased correlation leads to fatter tails in the distribution of the number of successful projects in the portfolio (see Online Supplement B), which in turn adversely affects the credit profile of the debt tranches and the risk-reward profile of the equity tranche.

EXHIBIT 2

Drug Development Process as a Multi-State Markov Chain



NOTES: Each state corresponds to a phase of development. At each phase, pipeline drugs have some probability of advancing to the next higher phase. Drugs that do not successfully advance are discontinued from any further development.

ABBREVIATION: NDA, New Drug Application.

EXHIBIT 3

Parameters Used to Simulate a Megafund with a Rare Disease Portfolio

	Distribution	Parameters	Pre-Clinical	Phase 1	Phase 2	Phase 3
Upfront Cost ($ millions)	Fixed	Constant	3.71			
Milestone Cost ($ millions)	Fixed	Constant		3.75	10.00	
Clinical Trial Cost ($ millions)	Bounded log-normal	Mean	2.80	3.03	7.64	
		Standard deviation	2.29	2.51	7.52	
		Upper Bound	10.00	20.00	50.00	
Duration (years)[a]	Log-normal	Mean	2.34	2.14	3.09	
		Standard Deviation	1.17	3.79	2.82	
Value ($ millions)	Bounded log-normal	Mean	7.66	24.20	57.80	321.50
		Standard Deviation	9.18	28.99	69.24	385.11
		Upper Bound	20.00	60.00	200.00	1000.00
		Pairwise Correlation	0.20	0.20	0.20	0.20
Phase Transition[a]	Bernoulli	Mean	0.795	0.759	0.488	
		Pairwise Correlation	0.20	0.20	0.20	0.20

NOTE: [a]Parameters for phase 1 and phase 2 based on estimates reported by Wong, Siah, and Lo (2019).

In this paper, we extend our framework to account for this dependence among drug development projects. We introduce a single-factor model with a Gaussian copula to model correlations among pipeline drugs (see Online Supplement A). This approach allows us to generate correlated phase transitions in our simulations, thus evaluating the probability of default and the financial performance of the RBO more accurately.

We use the parameters proposed by Fagnan et al. (2015) for a rare disease portfolio (see Exhibit 3). In addition, we update the parameters for duration and phase transitions based on the empirical estimates reported by Wong, Siah, and Lo (2019) in a recent study using two large pharmaceutical databases to determine the success rates of clinical trials. Compared to the parameters used in Fagnan et al. (2015), our recalibrated simulation results in longer clinical development times (0.6 years longer in phase 1 and 1.1 years longer in phase 2), and lower probabilities of success (14 percentage points lower for phase 1 and 9 percentage points lower for phase 2).

In our simulation, we assume a relatively conservative value of 0.20 for pairwise correlation in phase transitions among drug development projects. Although a literature search has not found any estimates of historical correlation among drug development projects, we believe that the correlation among orphan drugs is likely to be weak, given that a large proportion of orphan diseases have monogenic pathologies that act through largely unrelated mechanisms (Fagnan et al. 2014; Maher 2008). Furthermore, appropriate portfolio selection protocols can effectively minimize the correlation among assets. By limiting the maximum number of projects that can be acquired per indication group and target family, we can ensure that pipeline drugs in the portfolio are as dissimilar as possible, and any risks of failure are largely idiosyncratic in nature. In later sections, we also perform a sensitivity analysis of our results over a range of probabilities of success and pairwise correlation values.

RESULTS

Simulation

We performed three sets of experimental simulations of an orphan drug megafund. In the first, we simulated the performance of a "vanilla" megafund as outlined in Methods. In the second, we considered an RBO structure identical to the first,

except that it incorporates an additional credit enhancement mechanism proposed by Fagnan et al. (2013). We assumed that a third party is willing to take on some of the downside risk to debtholders by providing a guarantee for part of the debt issued, up to a maximum value of $100 million. This funding guarantee serves as a form of collateral that can be used to make up any shortfall in cash flow to meet debt obligations during the tenor of the fund. This type of external credit support may be provided to the megafund by a government agency, a private foundation, or even a patient advocacy group to advance a scientific or medical cause (e.g., drug development for a specific rare disease).

In our third experiment, we considered for comparative purposes an all-equity financing structure, while keeping all other modeling assumptions unchanged, to demonstrate the advantages of leverage and diversification. We assumed that this megafund begins with an initial amount of capital of $275 million, the size of the equity tranche in the first two sets of experiments. With a smaller pool of investable capital, the equity-only fund can only afford to acquire and finance 11 pre-clinical compounds for its portfolio, as opposed to 23 in the other two experiments.

For each experiment, we performed 2 million Monte Carlo simulated paths of drug development, drawing from the random distributions parameterized in Methods for each realization. By aggregating the results for each RBO structure—vanilla, guarantee-backed, and equity-only—we computed the risk profile of the debt tranches, the distribution of returns of the equity tranche, the expected cost of guarantee, and the impact of the research, quantified by the number of compounds sold in phases 2 and 3. The results are summarized in Exhibits 4 and 5.

We found that the risk of bond default was very small for both the senior and junior debt tranches under the vanilla megafund structure. The probability of default for the senior tranche was less than 1 basis point (bp), comparable to the historical default rate of AAA-rated corporate bonds. The default rate of the mezzanine tranche was higher at 55 bps, but still well below the average default rate of investment-grade corporate bonds over the same time horizon (see Online Supplement C). With the addition of a third-party funding guarantee, the default rates of both tranches fell to zero. This effectively makes the junior tranche a second senior tranche. Therefore, we combined both debt tranches in the guarantee-backed megafund into a single senior debt issue in our treatment. Despite the high face value of the guarantee, we noted that the expected cost to the guarantor was actually very small, about $37,000.

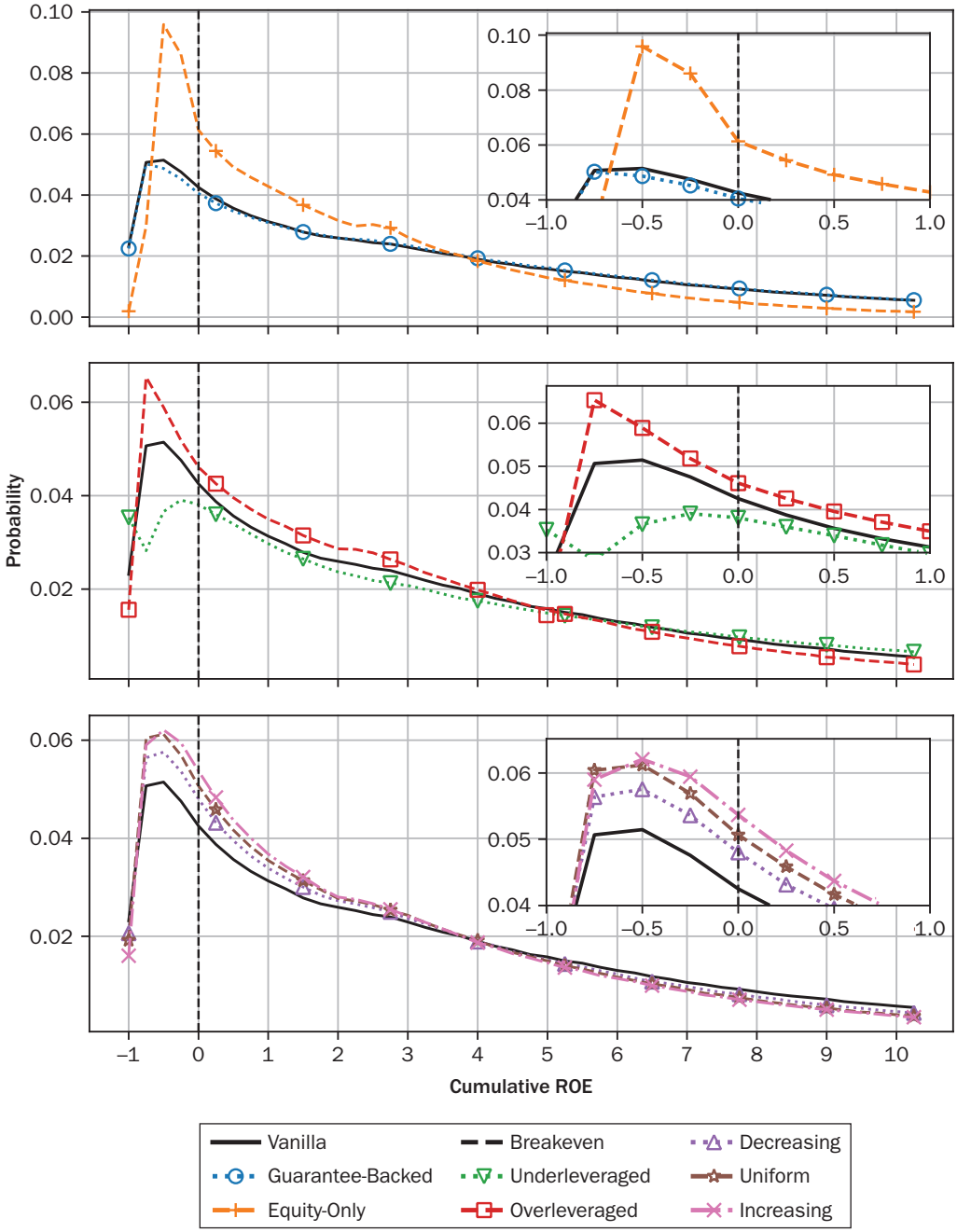
The vanilla megafund outperformed the all-equity financing structure in equity returns. It achieved an expected annualized return on equity (ROE) of 11.0%, 2.8 percentage points higher than that of the equity-only fund. Moreover, the probability of substantial gains, defined as an annualized ROE in excess of 25%, was four times higher under the standard structure (14.4%) than the equity-only fund (3.6%). Its Sharpe ratio, however, was about 3 percentage points lower in comparison.

Although the chances of a wipeout in the leveraged megafund were slightly higher than in the all-equity structure (0.6% versus 0.0%), the probability of a loss to equity was lower overall (19.4% versus 24.5%). In general, we found that distribution of cumulative ROE had a fatter left tail under the all-equity structure than under the vanilla structure (see Exhibit 4), suggesting that the use of leverage helps to reduce the downside risk and improve the upside potential.

With the addition of a funding guarantee, we observed a modest improvement in the return profile. The probability of loss fell further to 18.7%, while the expected annualized ROE improved slightly to 11.5%. The Sharpe ratio for the guarantee-backed structure was also the highest among the three RBO structures (66.1%), suggesting that the presence of a guarantee can help to reduce volatility without compromising returns. As a reference point, the average return and corresponding Sharpe ratio of the Center for

EXHIBIT 4

Distributions of Cumulative ROE for Different RBO Structures (top), Capital Structures (middle), and Acquisition Strategies (bottom)



NOTES: We truncate the distributions when cumulative ROE equals 10x for better visualization. The distributions demonstrate a positive skew with higher-than-normal kurtosis (leptokurtic).

ABBREVIATIONS: ROE, return on equity; RBO, research-backed obligation.

Research in Security Prices (CRSP) value-weighted index between 1970 and 2016 were 10.9% and 37%, respectively (Hull, Lo, and Stein 2019).

Among the three RBO structures, the leveraged structure performed best in terms of research impact. On average, 9.5 out of 23 pre-clinical projects in the vanilla

megafund portfolio reached either phase 2 or phase 3 by the end of the simulation horizon; the rest were discontinued or sold at earlier phases. In contrast, the equity-only fund started with 11 investigational compounds in its portfolio, out of which only 4.1 were successfully liquidated at either phase 2 or phase 3, less than half that of its leveraged counterpart.

Sensitivity Analysis

We performed a sensitivity analysis of our results with respect to several key parameters in our framework, namely the capital structure, the acquisition strategy, and the correlation and probability of success at phase transition.

Capital structure. In the previous section, we assumed a relatively well-balanced capital structure with a debt-to-equity ratio of 1.09 for the vanilla megafund. To examine the impact of different capital structures on performance, we considered two additional configurations. The first assumed an underleveraged capital structure with the same amount of equity as the vanilla case ($275 million), but half as much debt ($150 million). The second assumed an overleveraged structure, also with the same amount of equity as the vanilla case ($275 million), but with twice as much debt ($600 million). The resulting debt-to-equity ratios for the underleveraged megafund and the overleveraged megafund were 0.55 and 2.18, respectively. We summarize their performance in Exhibits 4 and 5.

We found that the risk of bond default generally increased with the leverage ratio of the capital structure. In the underleveraged megafund, the equity tranche (the tranche that absorbs the first loss to capital) was almost twice as large as the debt tranches combined. This high level of overcollateralization allowed the fund to remain solvent over a wide range of portfolio losses. Assuming a zero-coupon bond, the underleveraged megafund could lose up to 62% of its portfolio and still have enough capital to repay all of its debt obligations.

In contrast, the size of the equity tranche in the overleveraged megafund was less than half that of the debt tranches. Consequently, a small shock to the portfolio could easily wipe out the entire equity tranche and force the megafund into default. Assuming a zero-coupon bond, the overleveraged megafund must not lose more than 26% of its portfolio in order to have sufficient funds to redeem its bonds. The probabilities of default were therefore much larger for the overleveraged capital structure than for the balanced and underleveraged structures.

By issuing more debt, the overleveraged megafund could acquire and finance a larger number of projects (35 versus 17 for the underleveraged megafund). With a larger and therefore more diversified portfolio, its expected ROE was correspondingly higher. Its Sharpe ratio, however, was the lowest among the three capital structures, suggesting that the improvement in returns was outweighed by the increase in volatility associated with the use of greater leverage. We observed the opposite for the underleveraged megafund, which had the lowest expected ROE but the highest Sharpe ratio.

The megafund demonstrated very different risk-reward characteristics under each of these capital structures. In general, the use of leverage helped to improve the performance of the megafund. However, it came at the cost of increased risk to bondholders and also greater volatility in returns. The capital structure of a megafund should therefore be carefully selected to maximize the ROE while keeping the Sharpe ratio and default rates attractive to equity holders and fixed-income investors. To avoid under-borrowing and over-borrowing, the leverage ratio should be optimized based on the cost, value, and risk profiles of the underlying assets in the portfolio.

Acquisition strategy. In the next step of our sensitivity analysis, instead of assuming that all assets are acquired at the start of the simulation, we considered an

alternative strategy in which a small number of projects is acquired each period until the target capacity is reached (i.e., the portfolio is built up over time). Under some conditions, this strategy may be a more realistic example of a potential business model for an orphan drug megafund. The earlier assumption is useful if there is a large pool of projects that is readily available for immediate investment, for example, the rare diseases therapeutic development program at the National Center for Advancing Translational Sciences (Fagnan et al. 2015). In other cases, there may not be enough projects of sufficient quality on the market to create a strong and well-diversified portfolio.

Instead of settling for mediocre opportunities, a strategy of rolling acquisitions gives portfolio managers more time to source, evaluate, and identify promising clinical assets for acquisition. This approach leaves room for potential investment in breakthroughs that may emerge after the inception of the fund. Moreover, it aligns with the typical operation of translational drug development grant programs, which screen a large number of proposals annually, while enrolling only a few high-potential projects that have innovative scientific approaches or target unmet clinical needs.

Here, we considered three different acquisition patterns. We assumed that the vanilla megafund either made a monotonically increasing number of acquisitions each period, a uniform number, or a monotonically decreasing number, until the portfolio contained 23 projects. We found that the expected annualized ROE and research impact were smaller under rolling acquisitions than under our original assumption (see Exhibit 5). This was not surprising, since each stage of drug development requires a certain amount of time for clinical testing. Under a rolling acquisition strategy, a part of the portfolio is acquired after the first period. These projects are generally financed and developed for a shorter duration than those acquired at the beginning. As a result, they are less likely to complete phase 2 within the time horizon of the simulation before the portfolio must be liquidated. The probability of default in the junior tranche is consequently lower, because fewer risky late-stage drug development programs need to be funded. (The probability of transition is the lowest for phase 2 to phase 3.) As a trade-off, the expected ROE is also smaller because more drugs are sold before they can reach phase 3, which has the highest sale value. The effect is greatest under the monotonically increasing pattern, in which the largest part of the portfolio is acquired later in the simulation.

Correlation and probability of success. Finally, we investigated the sensitivity of our results to different pairwise correlations in phase transitions and the probabilities of success. We varied the correlation between 0% and 40%, and adjusted the probabilities of success for all phases by –10%, 0%, and +10%. For each combination of RBO structure, correlation value, and adjustment to the probability of success, we performed 100,000 Monte Carlo simulation paths. We summarize the results in Exhibits 6, 7, 8, and 9.

Intuitively, we expected the number of projects that reach phase 3 to increase with the probability of success. We also observed a corresponding increase in expected returns with higher adjusted phase transition probabilities, since the sale value of assets is substantially higher for late-stage projects than for early-stage drugs in the pipeline. As shown in in Exhibits 6, 7, and 8, a relative adjustment of +10% to the baseline probability of success at each stage of development improved the expected annualized ROE of the vanilla megafund by 4 percentage points, while the same adjustment in the opposite direction reduced the ROE by about 4.3 percentage points. We observed similar trends for the guarantee-backed and the equity-only megafunds.

In Exhibit 9, we plot the distribution of cumulative ROE for the different RBO structures, correlations, and adjustments to the probabilities of success. Because correlated projects tend to have similar outcomes, we found that the risk of tail

EXHIBIT 5

Performance of Each RBO Structure over 2 Million Monte Carlo Simulation Paths

	RBO Structure							
	Vanilla	Guarantee-Backed	Equity-Only	Under-Leveraged	Over-Leveraged	Decreasing[c]	Uniform[d]	Increasing[e]
STRUCTURE								
Capital								
Total ($ millions)	575	575	275	425	875	575	575	575
Senior Tranche ($ millions)	250	300		125	500	250	250	250
Junior Tranche ($ millions)	50			25	100	50	50	50
Equity Tranche ($ millions)	275	275	275	275	275	275	275	275
Guarantee								
Total ($ millions)		100						
Portfolio								
Number Acquired at Pre-Clinical	23	23	11	17	35	23	23	23
PERFORMANCE								
Senior Tranche								
Prob. of Default (bp)	0.8	0.0		0.0	26.9	0.1	0.0	0.0
Expected Loss (bp)	0.0	0.0		0.0	1.7	0.0	0.0	0.0
Junior Tranche								
Prob. of Default (bp)	54.8			4.0	266.1	30.9	21.5	13.7
Expected Loss (bp)	16.1			0.7	143.7	7.3	4.6	2.6
Equity Tranche								
Expected Cumulative ROE	3.8	3.8	2.1	3.0	5.0	3.2	2.9	2.8
Cumulative ROE SD	4.5	4.5	2.7	3.6	5.9	4.0	3.7	3.5
Cumulative ROE Skewness	1.6	1.6	1.6	1.5	1.8	1.6	1.6	1.6
Cumulative ROE Kurtosis	3.3	3.2	3.1	3.1	4.1	3.4	3.4	3.4
Expected Ann. ROE (%)	11.0	11.5	8.2	9.8	11.5	9.9	9.3	9.2
Sharpe Ratio[a] (%)	58.2	66.1	61.2	62.6	42.6	56.6	54.7	56.6
Prob. of Ann. ROE = −1.00 (%)	0.6	0.3	0.0	0.1	2.7	0.3	0.2	0.2
Prob. of Ann. ROE < 0.00 (%)	19.4	18.7	24.5	21.5	15.8	21.3	22.4	22.4
Prob. of Ann. ROE > 0.10 (%)	59.2	60.4	46.1	54.7	64.1	55.3	53.0	51.9
Prob. of Ann. ROE > 0.25 (%)	14.4	14.7	3.6	8.9	21.7	10.8	8.9	8.2
Guarantee								
Prob. of Draw (%)		0.3						
Expected Cost[b] ($ thousands)		37.4						
Research Impact								
Number Sold in Phase 2	5.3	5.1	1.5	3.2	10.2	5.0	4.6	4.9
Number Sold in Phase 3	4.2	4.3	2.6	3.6	4.9	3.7	3.4	3.2

NOTES: [a]Risk-free rate 2.0%; [b]Net present value at 2.0% discount rate; [c]Monotonically decreasing asset acquisition (nine in the first, seven in the second, five in the third, and two in the fourth); [d]Uniform asset acquisition (six in the first three, five in the fourth); [e]Monotonically increasing asset acquisition (three in the first, five in the second, seven in the third, and eight in the fourth).

ABBREVIATIONS: RBO, research-backed obligation; Prob., probability; bp, basis point; ROE, return on equity; SD, standard deviation; Ann., annualized.

events generally increased with the correlation among projects in the portfolio. This can be seen from the large positive skew and the heavy tails that highly correlated portfolios show in their distributions. We observed improvements in the expected cumulative ROE when the correlation was increased, but this was likely the effect of outliers in the right tail—that is, rare events where a large number of correlated projects reached phase 3 simultaneously, thus giving rise to extremely high returns. The mean of the annualized ROE was less sensitive to these outliers (see Online

EXHIBIT 6

Sensitivity of the Vanilla RBO Performance to Different Pairwise Correlations between Phase Transitions and Probabilities of Success

		0.9*p*					1.0*p*					1.1*p*				
	ρ	0.0	0.1	0.2	0.3	0.4	0.0	0.1	0.2	0.3	0.4	0.0	0.1	0.2	0.3	0.4
Senior Tranche																
Prob. of Default (bp)		1.2	0.9	0.9	1.1	0.9	1.0	0.5	0.5	0.4	0.4	0.2	0.5	0.4	0.6	0.5
Expected Loss (bp)		0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
Junior Tranche																
Prob. of Default (bp)		41.1	71.1	99.6	118.2	131.8	20.3	36.0	54.1	75.3	87.3	9.9	16.6	26.5	37.5	49.8
Expected Loss (bp)		15.1	20.7	24.7	27.6	28.8	8.6	12.5	16.0	19.3	20.7	4.6	6.7	9.1	11.8	13.6
Equity Tranche																
Expected Cumulative ROE		2.0	2.4	2.7	3.1	3.4	3.1	3.4	3.8	4.1	4.4	4.4	4.7	5.0	5.3	5.5
Cumulative ROE SD		2.5	3.3	4.0	4.6	5.1	3.0	3.8	4.5	5.0	5.5	3.6	4.4	5.0	5.5	5.9
Cumulative ROE Skewness		1.5	1.7	1.8	1.8	1.8	1.3	1.5	1.6	1.6	1.5	1.1	1.4	1.4	1.4	1.3
Cumulative ROE Kurtosis		2.8	4.2	4.5	4.3	3.7	2.1	3.2	3.3	3.0	2.6	1.7	2.4	2.4	2.2	1.9
Expected Ann. ROE (%)		7.8	7.2	6.7	6.3	6.2	11.9	11.4	11.0	10.6	10.3	15.7	15.3	15.0	14.7	14.3
Sharpe Ratio[a] (%)		46.8	33.6	26.1	22.1	20.0	92.9	71.4	58.5	49.2	44.3	142.1	117.4	99.0	86.0	76.0
Prob. of Ann. ROE = −1.00 (%)		0.4	0.7	1.1	1.3	1.4	0.2	0.4	0.6	0.8	1.0	0.1	0.2	0.3	0.4	0.5
Prob. of Ann. ROE < 0.00 (%)		20.9	26.1	29.2	31.5	33.3	10.9	15.9	19.3	22.2	24.4	5.3	8.3	11.3	13.8	16.1
Prob. of Ann. ROE > 0.10 (%)		46.4	47.3	48.0	48.6	49.2	62.2	60.3	59.3	58.8	58.5	76.0	72.6	70.4	69.0	67.9
Prob. of Ann. ROE > 0.25 (%)		2.6	6.2	9.4	12.4	15.2	6.7	10.9	14.5	17.5	20.2	14.2	18.2	21.3	23.8	26.0
Research Impact																
Number Sold in Phase 2		4.3	4.4	4.5	4.5	4.6	5.2	5.3	5.3	5.4	5.4	6.2	6.2	6.3	6.3	6.3
Number Sold in Phase 3		2.5	2.9	3.2	3.6	3.9	3.6	3.9	4.2	4.6	4.9	4.8	5.1	5.4	5.7	5.9

NOTES: [a]Risk-free rate 2.0%. The results are based on 100,000 Monte Carlo simulation paths for each combination of pairwise correlation and probability of success.

ABBREVIATIONS: ρ, pairwise correlation between phase transitions; *p*, probabilities of success for pre-clinical, phase 1, and phase 2; Prob., probability; bp, basis point; ROE, return on equity; SD, standard deviation; Ann., annualized.

Supplement D). In fact, the Sharpe ratio demonstrates an inverse relationship to the correlation (see Exhibits 6, 7, and 8), indicating that greater correlation actually led to lower annualized returns and greater volatility.

In most cases, the vanilla megafund outperformed the equity-only structure, except in the worst-case scenario, where the probabilities of success were low and the correlation among projects was high. The expected number of successful projects was small under this set of parameters; thus, it is unlikely that the megafund could generate sufficient cash flow to sustain its debt obligations and investment activities under these conditions. The high level of correlation further exacerbated the situation by introducing substantial systematic risk to the portfolio. It is clear that, given the risk profile of the underlying portfolio, the megafund is overleveraged. In such cases, a better performing megafund could be created by either adopting a more appropriate capital structure or securing some form of funding guarantee, that is, the guarantee-backed structure.

Despite the variation in parameter values, the probability of default for the senior tranche remained below 1 bp in almost all scenarios. This can be attributed to the credit enhancement mechanisms adopted in the RBO structure, including the subordination of cash flows and the interest coverage tests to trigger early liquidation during periods of illiquidity. The risk of default for the junior tranche, however, was very sensitive to changes in either parameter. Like the trends observed in equity returns, the risk of default increased with the level of correlation among projects

EXHIBIT 7

Sensitivity of the Guarantee-Backed RBO Performance to Different Pairwise Correlations between Phase Transitions and Probabilities of Success

		0.9*p*					1.0*p*					1.1*p*				
	ρ	0.0	0.1	0.2	0.3	0.4	0.0	0.1	0.2	0.3	0.4	0.0	0.1	0.2	0.3	0.4
Senior Tranche																
Prob. of Default (bp)		0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
Expected Loss (bp)		0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
Equity Tranche																
Expected Cumulative ROE		2.1	2.4	2.8	3.1	3.5	3.2	3.5	3.9	4.2	4.5	4.5	4.8	5.1	5.3	5.6
Cumulative ROE SD		2.5	3.3	4.0	4.6	5.1	3.0	3.8	4.5	5.1	5.6	3.7	4.4	5.0	5.5	5.9
Cumulative ROE Skewness		1.4	1.7	1.8	1.8	1.7	1.2	1.5	1.6	1.6	1.5	1.1	1.3	1.4	1.3	1.3
Cumulative ROE Kurtosis		2.6	4.2	4.6	4.2	3.6	1.9	3.2	3.2	2.9	2.6	1.6	2.4	2.3	2.1	1.9
Expected Ann. ROE (%)		8.2	7.7	7.5	7.3	7.3	12.3	11.8	11.5	11.2	11.1	16.0	15.6	15.3	15.1	14.8
Sharpe Ratio[a] (%)		54.0	41.1	35.1	31.1	29.3	99.1	78.5	66.0	58.7	54.1	147.5	122.8	105.8	94.2	84.9
Prob. of Ann. ROE = −1.00 (%)		0.3	0.4	0.4	0.5	0.5	0.2	0.2	0.3	0.4	0.4	0.1	0.1	0.2	0.2	0.2
Prob. of Ann. ROE < 0.00 (%)		19.7	25.2	28.4	30.9	32.7	10.2	15.0	18.6	21.5	23.9	4.8	7.8	10.7	13.4	15.8
Prob. of Ann. ROE > 0.10 (%)		47.7	48.3	49.1	49.6	50.2	63.6	61.5	60.4	59.7	59.4	77.5	73.8	71.7	70.1	68.9
Prob. of Ann. ROE > 0.25 (%)		2.6	6.3	9.6	12.6	15.5	6.8	11.2	14.7	17.8	20.5	14.7	18.6	21.7	24.3	26.7
Guarantee																
Prob. of Draw (%)		0.3	0.4	0.4	0.5	0.5	0.2	0.2	0.3	0.4	0.4	0.1	0.1	0.2	0.2	0.2
Expected Cost[b] ($ thousands)		33.7	38.6	41.4	44.1	45.3	26.8	31.8	35.0	37.0	35.5	18.8	21.9	25.8	27.2	29.0
Research Impact																
Number Sold in Phase 2		4.2	4.2	4.3	4.4	4.4	5.1	5.1	5.1	5.2	5.2	6.0	6.0	6.1	6.1	6.1
Number Sold in Phase 3		2.6	2.9	3.3	3.6	4.0	3.6	4.0	4.3	4.6	4.9	4.9	5.2	5.5	5.7	6.0

NOTES: [a]Risk-free rate 2.0%; [b]Net present value at 2.0% discount rate. The results are based on 100,000 Monte Carlo simulation paths for each combination of pairwise correlation and probability of success.

ABBREVIATIONS: ρ, pairwise correlation between phase transitions; *p*, probabilities of success for pre-clinical, phase 1, and phase 2; Prob., probability; bp, basis point; ROE, return on equity; SD, standard deviation; Ann., annualized.

when there was a greater probability of loss, but decreased with the probabilities of success when there was a greater probability of profit. With a funding guarantee in place, the probability of default for the guarantee-backed megafund was consistently kept below 0.1 bp. The expected cost to the guarantee also increased with the level of correlation and decreased with the probabilities of success.

In general, we found that the performance of the megafund became less attractive when correlation among projects was introduced. Nevertheless, the vanilla megafund outperformed the all-equity structure over a wide range of probabilities of success and correlation, except in cases where there was substantial deviation from the presumed values. In those scenarios, the capital structure and leverage ratio need to be re-optimized with respect to the risk profile of the underlying portfolio. The use of a funding guarantee can also greatly improve the performance of the megafund. Overall, the risk of default for the senior tranche remained close to zero even when large correlations and small probabilities of success were assumed.

CONCLUSION

Traditional financing models generally have struggled to support early-stage drug development, which corresponds to the riskiest and most challenging part of the drug approval process. Due to the lack of funding, early-phase translational research is

EXHIBIT 8

Sensitivity of the Equity-Only RBO Performance to Different Pairwise Correlations between Phase Transitions and Probabilities of Success

		0.9*p*					1.0*p*					1.1*p*				
	ρ	0.0	0.1	0.2	0.3	0.4	0.0	0.1	0.2	0.3	0.4	0.0	0.1	0.2	0.3	0.4
Equity Tranche																
Expected Cumulative ROE		1.2	1.4	1.6	1.7	1.9	1.8	1.9	2.1	2.3	2.4	2.5	2.6	2.8	2.9	3.0
Cumulative ROE SD		1.7	2.1	2.4	2.7	2.9	2.0	2.4	2.7	3.0	3.2	2.4	2.7	3.0	3.2	3.4
Cumulative ROE Skewness		1.5	1.7	1.8	1.8	1.8	1.4	1.5	1.6	1.6	1.5	1.2	1.3	1.4	1.3	1.3
Cumulative ROE Kurtosis		2.9	4.1	4.4	4.3	3.9	2.4	3.0	3.2	3.1	2.7	1.9	2.3	2.3	2.1	1.9
Expected Ann. ROE (%)		5.2	5.5	5.9	6.2	6.6	8.0	8.0	8.2	8.4	8.6	10.8	10.7	10.7	10.7	10.7
Sharpe Ratio[a] (%)		37.1	37.8	39.4	40.8	42.3	69.6	63.8	61.3	59.8	59.4	106.8	93.7	86.4	81.6	78.4
Prob. of Ann. ROE = −1.00 (%)		0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
Prob. of Ann. ROE < 0.00 (%)		29.1	31.6	33.6	35.2	36.6	18.4	21.8	24.4	26.6	28.4	10.4	13.7	16.4	18.8	20.8
Prob. of Ann. ROE > 0.10 (%)		31.1	34.1	36.4	38.2	40.0	43.2	44.9	46.1	47.3	48.4	56.6	56.4	56.6	56.8	57.1
Prob. of Ann. ROE > 0.25 (%)		0.3	1.2	2.2	3.3	4.4	1.0	2.3	3.6	4.9	6.2	2.6	4.2	5.7	7.1	8.4
Research Impact																
Number Sold in Phase 2		1.2	1.2	1.2	1.3	1.3	1.4	1.5	1.5	1.5	1.6	1.8	1.8	1.8	1.8	1.9
Number Sold in Phase 3		1.7	1.9	2.0	2.2	2.4	2.3	2.5	2.6	2.8	3.0	3.0	3.2	3.3	3.4	3.6

NOTES: [a]Risk-free rate 2.0%. The results are based on 100,000 Monte Carlo simulation paths for each combination of pairwise correlation and probability of success.

ABBREVIATIONS: ρ, pairwise correlation between phase transitions; p, probabilities of success for pre-clinical, phase 1, and phase 2; Prob., probability; ROE, return on equity; SD, standard deviation; Ann., annualized.

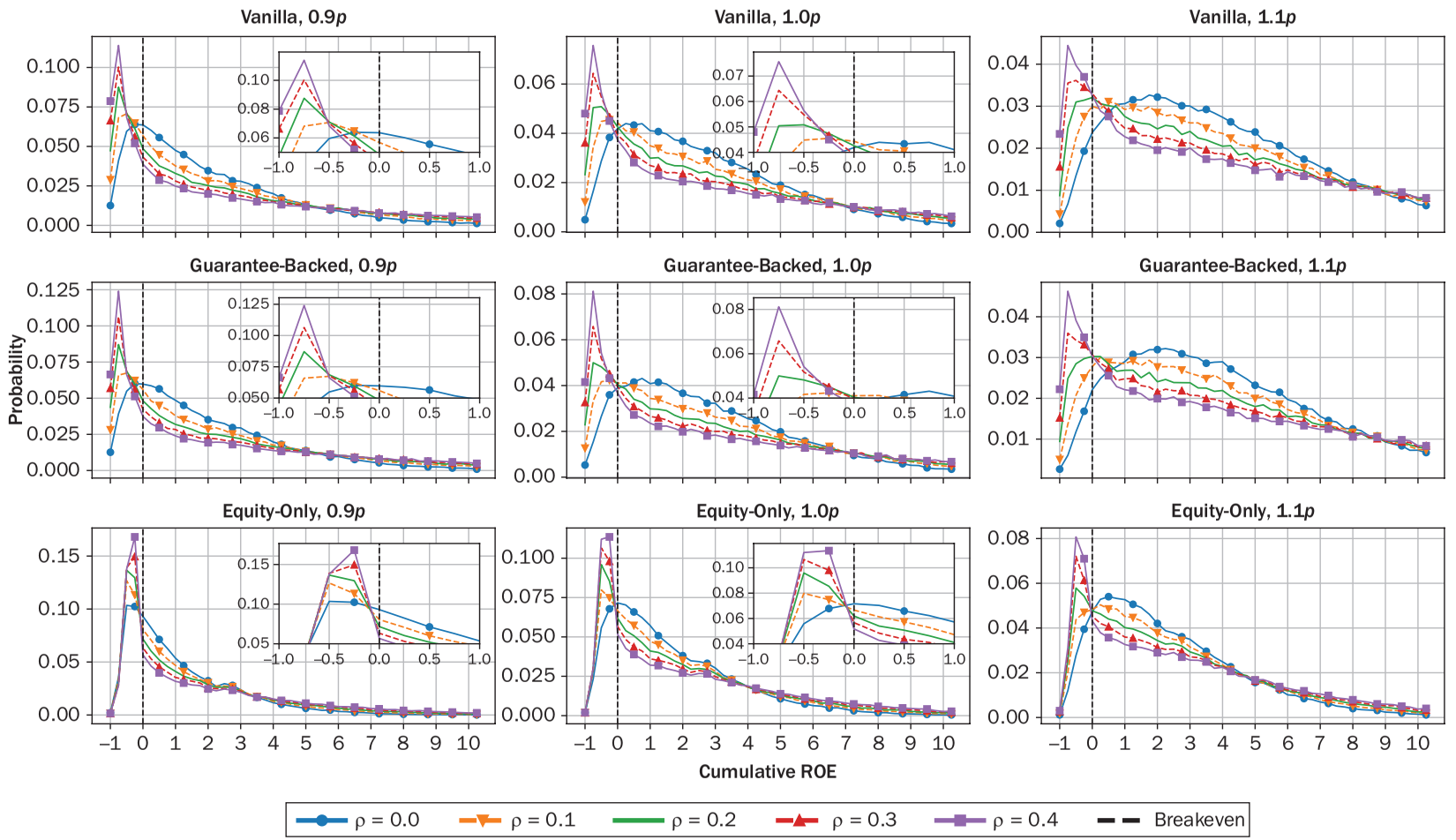
often referred to as the "Valley of Death" in the drug development pipeline. In this paper, we study an alternative financing model proposed by Fernandez, Stein, and Lo (2012)—an RBO structure funded using both debt and equity—for early-stage orphan drug development. We extend their framework to account for dependence among phase transitions in projects, thus making it a more realistic representation of biopharma R&D. Using a multi-state, multi-period simulation approach, we characterize the performance of different megafund structures over a wide range of assumptions.

We find that our vanilla megafund demonstrates risk-reward characteristics attractive to both fixed-income investors and equity holders. The default risks of its debt tranches are comparable to the historical default rates of AAA-rated corporate bonds. In addition, the expected returns and the Sharpe ratio of the vanilla megafund are promising when compared to the CRSP index. Because R&D projects typically have small betas (i.e., weak correlation with market returns), the RBO structure can be an attractive option to investors seeking to diversify their portfolios away from conventional instruments. Consistent with previous studies, our results also show that the performance of the megafund can be further improved with the addition of a funding guarantee. Although the face value of the considered guarantee is large, the expected cost to the guarantor is, in fact, very small.

We simulate an equity-only structure as a baseline for comparison with the vanilla megafund, and find that the latter outperforms the former both in terms of ROE and research impact (quantified by the number of compounds successfully sold in phases 2 and 3). The disparity in performance can be attributed to the use of leverage in the vanilla megafund, which allows it to acquire a larger and more diversified portfolio. As shown in in Exhibit 5, equity returns generally increase with leverage in the capital structure. However, we note that adding leverage increases the volatility and default risk of the megafund as well. Because of the trade-off between risk and return, greater leverage is not always better, and will therefore depend on the risk profile of the

EXHIBIT 9

Sensitivity of Cumulative ROE to Different Pairwise Correlations between Phase Transition and Probabilities of Success



NOTES: Each plot corresponds to a different combination of RBO structure and adjustment to the probability of success. We truncate the plots when cumulative ROE equals 10x for better visualization.

ABBREVIATIONS: ROE, return on equity; RBO, research-backed obligation; ρ, pairwise correlation between phase transitions; p, probabilities of success for pre-clinical, phase 1, and phase 2.

assets in the portfolio. The size of the debt tranches should be carefully selected to maximize the ROE while keeping the risk of default below thresholds acceptable to institutional investors.

In addition to the capital structure, we investigate the sensitivity of our results with respect to different project acquisition strategies, assuming a range of correlations and probabilities of success. We observe lower returns when the portfolio is constructed in stages over time instead of a single period at the start of simulation. This is explained by the projects acquired later having less time for development over the tenor of the megafund. In these cases, the use of more sophisticated securitization techniques like dynamic leverage (Montazerhodjat, Frishkopf, and Lo 2016) can help improve its performance.

In contrast with previous studies, we did not assume independence between phase transitions. The introduction of correlation leads to fatter tails in the distribution of returns, which imply higher probabilities of debt default and equity loss. However, we found that the senior tranche was protected by credit enhancement mechanisms from systematic risk even at high levels of correlation in the portfolio. In general, the vanilla and guarantee-backed megafunds outperformed the all-equity structure over a wide range of correlations and probabilities of success.

We emphasize that our simulation is based on specific modeling assumptions regarding the cost, duration, valuation, and transition probability of clinical trials at each stage of development (outlined in Exhibit 3). As seen in Exhibits 6, 7, and 8, the expected performance of the megafund can change materially when different parameter values are used. The usefulness of our results depends heavily on the accuracy of the parameter estimates.

Unfortunately, given the nature of biopharma R&D, model calibration is especially challenging. For example, drug development projects are notoriously difficult to value since domain experts tend to have conflicting opinions on the therapeutic potential and market value of investigational drugs. This is particularly common for first-in-class programs with novel treatment pathways. Furthermore, project outcomes are often dependent on factors that cannot be easily quantified, that is, the expertise and experience of the investigators and the managers in charge of the clinical trials.

In this paper, we used the empirical estimates proposed by Fagnan et al. (2015) based on industry averages and expert panel evaluations for a rare disease portfolio. We also updated the parameters for duration and phase transition based on a more recent study by Wong, Siah, and Lo (2019) using two large pharmaceutical databases. Our assumptions may be considered conservative, since they do not account for possibilities that can make orphan drug development less costly or more lucrative, that is, adaptive clinical trials that cost less and require shorter durations, or priority review vouchers (PRVs) that can be sold for additional revenue. (As an illustration, GW Pharmaceuticals received a PRV from the U.S. Food and Drug Administration for developing Epidiolex, a drug that treats rare childhood epilepsy. It sold the PRV to Biohaven Pharmaceutical for $105 million in March 2019 [GW Pharmaceuticals plc 2019].)

We should note that the investment mandate of the megafund outlined in this paper is related to, but differs from, that of the “biopharmaceutical mega-fund” proposed by Ortiz, Stone, and Zissu (2020). We considered the financing of a portfolio of risky early-stage pre-clinical assets, in contrast to their objective of securitizing a large pool of phase 1 assets. In addition, they investigated the potential benefits of incorporating assets backed by revenue-generating licensing and royalty agreements with well-capitalized entities. Other related studies include Yang et al. (2016), who demonstrated the importance of empirical validation in selecting projects for a cancer megafund, and Mishra et al. (2018), who proposed a novel “cryptocurrency megafund” structure to alleviate adverse selection and moral hazards from information asymmetry and misaligned utilities among biomedical stakeholders and investors.

Also, despite our focus on orphan drugs in this paper, our framework can be easily generalized to arbitrary drug development portfolios once the simulation parameters are modified accordingly (see https://projectalpha.mit.edu for details and open-source simulation software).

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K.S. reports no conflicts.

A.L. reports personal investments in private biotech companies, biotech venture capital funds, and mutual funds. A.L. is a co-founder and partner of QLS Advisors, a healthcare analytics and consulting company; an advisor to BrightEdge Ventures and Thales; a director of BridgeBio Pharma, Roivant Sciences, and Annual Reviews; chairman emeritus and senior advisor to AlphaSimplex Group; and a member of the Board of Overseers at Beth Israel Deaconess Medical Center and the NIH's National Center for Advancing Translational Sciences Advisory Council and Cures Acceleration Network Review Board. During the most recent six-year period, A.L. has received speaking/consulting fees, honoraria, or other forms of compensation from: AIG, AlphaSimplex Group, BIS, BridgeBio Pharma, Citigroup, Chicago Mercantile Exchange, Financial Times, FONDS Professionell, Harvard University, IMF, National Bank of Belgium, Q Group, Roivant Sciences, Scotia Bank, State Street Bank, University of Chicago, and Yale University.

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