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Financially adaptive clinical trials via option pricing analysis

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ABSTRACT

The regulatory approval process for new therapies involves costly clinical trials that can span multiple years. When valuing a candidate therapy from a financial perspective, industry sponsors may terminate a program early if clinical evidence suggests market prospects are not as favorable as originally forecasted. Intuition suggests that clinical trials that can be modified as new data are observed, i.e., adaptive trials, are more valuable than trials without this flexibility. To quantify this value, we propose modeling the accrual of information in a clinical trial as a sequence of real options, allowing us to systematically design early-stopping decision boundaries that maximize the economic value to the sponsor. In an empirical analysis of selected disease areas, we find that when a therapy is ineffective, our adaptive financing method can decrease the expected cost incurred by the sponsor in terms of total expenditures, number of patients, and trial length by up to 46%. Moreover, by amortizing the large fixed costs associated with a clinical trial over time, financing these projects becomes less risky, resulting in lower costs of capital and larger valuations when the therapy is effective.

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1. Introduction

When discounted cash flow (DCF) analysis is used to value a project, we must model the possibility that, as the project unfolds, managers might expand the project if it goes well, or scale back or even abandon the project when it does not work out as forecasted. Intuitively, projects that can be modified as new information becomes available are more valuable than projects without this flexibility. Moreover, the more uncertain the outlook, the more valuable this flexibility becomes. The ability to modify a project in the future is known as a real option, and in this article we consider how option pricing analysis can be used to design financially-optimal decision boundaries for futility in adaptive clinical trials for drugs, medical devices, and other therapeutics.¹

Adaptive randomized clinical trials (ARCTs) are a specific type of controlled experiment in which a drug candidate is tested against the current standard of care. However, unlike traditional randomized clinical trials (RCTs)—in which the

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¹ For expositional convenience, our use of the term “drug” includes medical devices, diagnostics, and other therapeutics requiring regulatory approval.

1 sample sizes are fixed in advance and no conclusions are drawn prior to the completion of testing on the entire sample—
 2 ARCTs use Bayesian methods to evaluate the drug candidate's efficacy as each observation is collected.² If the cumulative
 3 evidence is statistically significantly positive (negative), the trial is terminated due to a determination of efficacy (futility),
 4 otherwise the next observation is drawn. In addition to considerations of statistical significance, at any point in time, the
 5 drug's sponsor knows the economic cost of the next observation, and must decide from a commercial perspective whether
 6 to proceed with the trial or stop early. Continuing the trial allows the sponsor to make future decisions about whether to
 7 continue or abandon after subsequent observations. In other words, the sponsor has the right—but not the obligation—to
 8 invest in future observations and stages of drug development. Therefore, these decision points can be evaluated as a
 9 sequence of real options.

10 The standard tools used to value financial options originate from [Black and Scholes \(1973\)](#) and [Merton \(1973\)](#). The term
 11 “real option” was first introduced to the literature by [Myers \(1977\)](#), who identified that many corporate assets can be
 12 viewed as call options. Option-pricing techniques have since been used to value a variety of managerial decisions including
 13 the option to expand, contract, defer, or abandon a project across a range of applications from natural resources to patents
 14 and R&D ([Brennan and Schwartz, 1985](#); [Titman, 1985](#); [McDonald and Siegel, 1985](#); [Trigeorgis and Mason, 1987](#); [Ingersoll
 15 and Ross, 1992](#); [Pindyck, 1993](#); [Moel and Tufano, 2002](#); [Schwartz, 2004](#); [Hsu and Schwartz, 2008](#); [Gunther McGrath and
 16 Nerkar, 2004](#); [Bogdan and Villiger, 2010](#); [Lynch and Shockley, 2016](#); [Vasseur and Pérez, 2016](#)), and has also been applied
 17 directly to the valuation of companies and assets in the biotechnology and pharmaceutical industries ([Myers and Howe,
 18 1997](#); [Kellogg and Charnes, 2000](#); [Banerjee, 2003](#); [Schwartz, 2004](#); [Hsu and Schwartz, 2008](#); [Harmann and Hassan, 2006](#);
 19 [Vasseur and Pérez, 2016](#)). However, none of these studies have applied real option theory to the valuation of RCT or ARCT
 20 outcomes.

21 Despite the novelty of our theoretical framework, practitioners have already begun making use of “adaptive financing”
 22 structures in the biopharma industry. One example, highlighted by [Lo and Narahariseti \(2014\)](#), is the 2012 financing by
 23 Royalty Pharma of Sunesis Pharmaceuticals' Phase-3 adaptive clinical trial of its leukemia drug, Vosaroxin. In this trial
 24 design, an independent data safety monitoring board (DSMB) was responsible for ongoing collection and analysis of the
 25 clinical trial data and had sole authority to make changes in the trial design during the course of the study, including
 26 increasing the sample size. While Sunesis had sufficient capital to fund the original clinical trial of 450 patients, the
 27 company was seeking an additional \$25 million to fund the potential expansion to 675 patients if, during the interim, the
 28 drug showed a certain degree of efficacy. Royalty Pharma conditionally agreed to pay Sunesis the \$25 million in exchange
 29 for various payments tied to the outcomes of the trial and the decisions of the DSMB.³ This adaptive financing structure
 30 enabled Royalty Pharma to significantly limit its exposure to the risk of a negative outcome of the clinical trial and, at
 31 the same time, positioned it to receive a sizeable royalty in the event that Vosaroxin is approved. At the same time, this
 32 structure also allowed Sunesis to focus on preparing Vosaroxin's regulatory filings and U.S. commercial launch and to
 33 expand their development program, thereby reducing its risk as well.

34 This example highlights the two major factors that affect the value of a drug and, consequently, the value of real
 35 options. The first is scientific risk—will the drug meet its clinical endpoints? This risk is generally uncorrelated with
 36 macroeconomic factors, and is therefore considered idiosyncratic. The second is market risk: Even if successful from a
 37 scientific perspective, will the drug be commercially successful? For example, early-stage R&D projects are traditionally
 38 monetized through licensing, joint development deals, and mergers and acquisitions with other biopharma companies.
 39 Therefore, despite meeting their clinical endpoints, these drugs may face substantial systematic risk in the form of
 40 business- and credit-cycle downturns, when investor appetite for such assets is lower ([Thakor et al., 2017](#)). As a trial
 41 progresses, clinical observations and shifting market conditions provide information on both of these risks.

42 Our real options framework offers a systematic and computationally practical valuation framework that incorporates
 43 information contained in ongoing clinical observations to determine whether it is economically beneficial to continue or
 44 terminate a clinical trial.

45 2. The option value of a clinical trial

46 Management decisions during the drug development process depend on multiple parameters that may change over
 47 time as new information is collected. As time passes, and more data are collected, the sponsor will begin to develop
 48 a clearer understanding of a drug's economic potential. This clarity can manifest itself in a number of ways, including
 49 through the likelihood the drug will be able to meet its endpoints. The closer we get to the end of a clinical trial, the better
 50 informed we will be about the economic potential of the drug. For example, imagine a drug shows early signs of toxicity,
 51 reducing our forecasted sales and increasing the probability that it will not be approved for commercial development.
 52 After reevaluating the project, we may decide to abandon the drug because it is no longer profitable. To estimate the value
 53 of a project more accurately, we must model this risk directly.

² See, for example, [Berry \(1985, 1987, 1993, 2006\)](#) and [Jennison and Turnbull \(1999\)](#).

³ Specifically, in exchange for the \$25 million commitment, Sunesis agreed to pay Royalty Pharma 3.6% on future net sales of the drug if the study was stopped early for efficacy, or a 6.75% participation payment on future net sales plus two warrants if the sample size was increased. Each warrant would entitle Royalty Pharma to purchase 1,000,000 shares of Sunesis common stock at an exercise price of \$3.48 and \$4.64 per share, respectively. If the DSMB decided that the trial should continue as planned, Royalty Pharma would have the option of making the \$25 million investment upon the un-blinding of the study in exchange for a 3.6% participation payment on future net sales. See [Lo and Narahariseti \(2014\)](#) for further details.

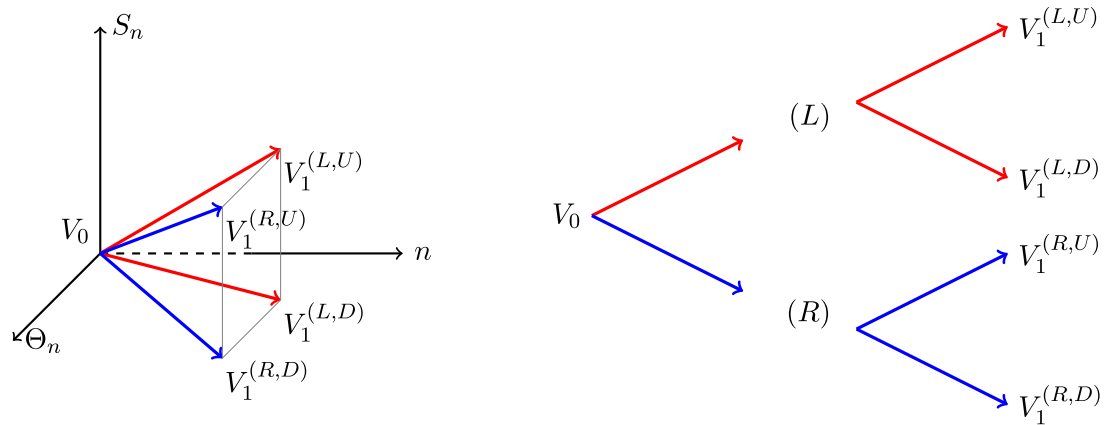


Fig. 1. A single step of the binomial lattice. The scientific risk, Θ_n , can either step left (L) or right (R) depending on the outcome of the most recent clinical evidence, and the market risk, S_n , can either step up (U) or down (D) depending on evolving market conditions. The right panel separates these two independent sources of risk into a two-step process.

Real option valuation techniques, such as the binomial option pricing model (Sharpe, 1978; Cox et al., 1979), attempt to model this risk by forecasting the possible trajectories the economic potential of a project can follow based on both scientific and market risks. Given an estimate of the current market potential, there is uncertainty about what that estimate will be one period from now. We can model the progress of this market estimate as new information is received using a recombining binomial lattice.

For a balanced two-arm RCT with a sample size of N patients in each arm, the possible trajectories of the summary statistic on the primary endpoint, Θ_n , can be represented as sample paths in this framework. The primary endpoint is the main measurement that a clinical trial is designed to assess (e.g., the magnitude of reduction of blood pressure between the treatment and control arms of an anti-hypertension drug trial). The subscript n denotes the collection of the n th observation, and represents a discrete event where new information about the primary endpoint is obtained. A new clinical observation of the effectiveness or safety of a new therapy can either be positive or negative, reflected by the left (L) and right (R) steps of the binomial lattice in Fig. 1. For example, if an anti-hypertension drug reduces the blood pressure of a patient in the investigational arm of a clinical trial by 10 mmHg, a clinically relevant improvement, this observation shifts the interim summary statistic, Θ_n , in the direction of statistical significance. Similarly, the state of the market, S_n , can independently improve (U) or deteriorate (D) with a certain probability. This risk represents changes to the economic potential of the drug (e.g., the present value of the drug's profits, assuming regulatory approval) due to external shocks in market factors including business- and credit-cycle risk, regulatory changes, and competition.

The right panel of Fig. 1 illustrates how this two-dimensional risk can be visualized as a binomial tree. First the summary statistic of the clinical trial is updated, followed by an update of market conditions. Suppose that at the start of the period, the cost of continuing the trial to the next clinical observation is K , and the sponsor has the option to continue or abandon the trial. In this scenario, the value of the therapy at the start of the period is given by:

$$V_0 = \max\left(0, \frac{E_0^Q[V_1]}{e^{r_f \Delta t}} - K\right), \quad (1)$$

where the risk-neutral probability measure is denoted by Q ,⁴ the risk-free rate by r_f , and the length of the period by Δt . Since we have assumed that scientific risk is independent of market risk, its risk-neutral probabilities are equal to its physical probabilities, and therefore (1) can be expressed as:

$$V_0 = \max\left(0, \frac{E_0^P[E_0^Q[V_1 | \Theta_1]]}{e^{r_f \Delta t}} - K\right), \quad (2)$$

where the physical probability measure is denoted by P . The calculation of a project's value then becomes straightforward.

Once all possible scenarios with their corresponding cash flows and various risk-neutral probabilities have been defined, we multiply the future values by their probabilities to calculate the expected future value under the risk-neutral measure, and then discount this expected cash flow at the risk-free rate back one layer. After we subtract the cost of continuing the trial, if the value at any node is negative, we abandon the project and set the value of the project at that node to \$0. In these states, the project value increases from a negative value to \$0. This difference in value is directly linked to the option to abandon.

⁴ See, for example, Duffie (2010) for details about risk-neutral pricing.

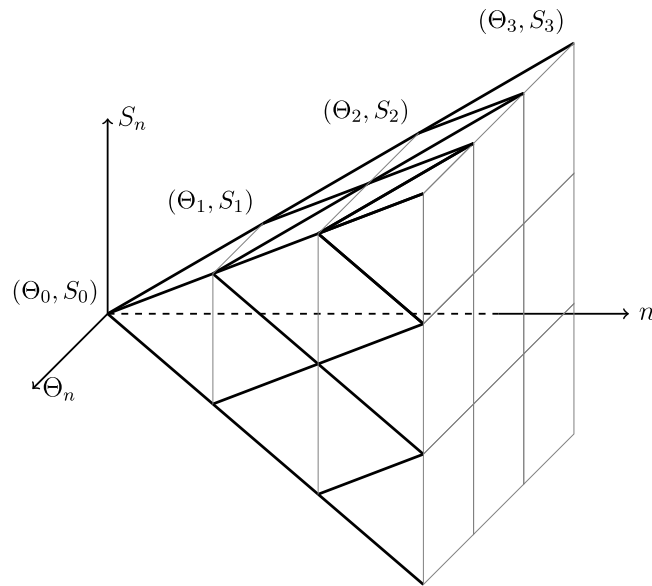


Fig. 2. Binomial lattice model. The further we proceed into the future, the less certain we are about the state of the market or the clinical trial, and the tree therefore branches out as we move forward in time.

The further we proceed into the future, the less certain we are about the state of the market or the clinical trial, and the tree therefore branches out as we move forward in time (see Fig. 2). The leaves of the tree represent the possible market states at the end of the clinical trial, which, for pivotal phase 3 trials, precedes product launch and, for early-stage trials, precedes a later-stage trial. Working backwards from the leaves of the tree to its root, we can calculate the value of the therapy at each node, one layer at a time. The present value of the project then corresponds to the value V_0 calculated recursively at the root node:

$$\begin{aligned}
 V_N &= \max\left(0, f(\Theta_N, S_N) - I\right) \\
 V_{N-1} &= \max\left(0, \frac{E_{N-1}^P[E_{N-1}^Q[V_N | \Theta_N]]}{e^{r_f \Delta t}} - K\right) \\
 &\vdots \\
 V_0 &= \max\left(0, \frac{E_0^P[E_0^Q[V_1 | \Theta_1]]}{e^{r_f \Delta t}} - K\right),
 \end{aligned} \tag{3}$$

where $f(\cdot)$ is a function that defines the economic value of a therapy at the end of the clinical trial for a given realization of (Θ_n, S_n) , and I is the investment required for the next stage of development. For example, for a phase 3 clinical trial, I would be the launch-related investment required to commercialize the drug upon regulatory approval.

The economic value of a drug upon commercial launch is often estimated by forecasting the drug's peak annual sales and sales curve over time given market conditions and the drug's attributes. This uncertainty is eventually resolved with the progression of the drug through the clinical trial as its safety and efficacy are revealed. In addition to these factors, future sales will be influenced by the growth rate of the target market, the marketing power of the company, other competing treatments available, the price elasticity for the disease, and so on. These cash flows must then be discounted at an appropriate cost of capital, which is often estimated as the expected rate of return investors will demand from projects with similar risk. While the appropriate discount rate will depend on factors such as investor risk aversion and the correlation of the project's cash flows with other investments, in general, the cost of capital will be higher in the earlier stages of drug development relative to the period after a successful commercial launch.

3. Defining scientific and market risk processes

To develop a better understanding of our valuation framework, consider a balanced two-arm RCT that uses the z-statistic as a measure of its primary quantitative endpoint. We assume that subjects in the treatment arm receive the investigational therapy and each subject's response is independent of all other responses. If an existing therapy is available, then this standard of care is assumed to be administered to the patients in the control arm. The response variables in the

treatment arm (i.e., the set of clinical outcomes as measured by the primary endpoint for patients in the treatment arm), denoted by $\{Y_1, \dots, Y_n\}$, are assumed to be independent and identically distributed, where $Y_i \sim \mathcal{N}(\mu_y, \sigma^2)$. Similarly, responses in the control arm, represented by $\{P_1, \dots, P_n\}$, are assumed to be independently and identically distributed as $P_i \sim \mathcal{N}(\mu_p, \sigma^2)$, where the response variance in each arm is known and equal to σ^2 . We confine ourselves to superiority trials where the investigational therapy is likely to have either a positive effect (i.e., the alternative hypothesis, $H = 1$), or no effect (i.e., the null hypothesis, $H = 0$). In such cases, the assumed treatment effect of the therapy under the alternative hypothesis, δ , is defined as the difference between the response means in the two arms (i.e., $\delta \equiv \mu_y - \mu_p$). We collect observations from the treatment and control arms, and form the following z-statistic (sometimes referred to as the Wald statistic):

$$Z_n = \frac{\sqrt{I_n}}{n} \sum_{i=1}^n (Y_i - P_i) \quad , \quad (4) \quad 10$$

where n is the number of observations collected in each arm, Z_n is a normal random variable, i.e., $Z_n \sim \mathcal{N}(\delta\sqrt{I_n}, 1)$, and $I_n = \frac{n}{2\sigma^2}$ is the information in the trial (Jennison and Turnbull, 1999).

Given an observation $Z_n = z_n$, we define the likelihood ratio of z_n , $\Lambda(z_n)$, as

$$\Lambda(z_n) = \frac{\Pr(Z_n = z_n \mid H = 0)}{\Pr(Z_n = z_n \mid H = 1)} \quad . \quad (5) \quad 14$$

Taking the natural logarithm of the likelihood ratio function and using (4) to substitute in for Z_n , the log-likelihood function, $\ln \Lambda(Z_n) \equiv \Theta_n$, can be expressed as a random walk (Gallager, 2014),

$$\Theta_n = \sum_{i=1}^n X_i \quad , \quad \text{where } X_i = \frac{\delta^2 - 2\delta(Y_i - P_i)}{4\sigma^2} \quad , \quad (6) \quad 17$$

and Θ_n is defined to be the scientific risk process. The mean displacement (i.e., drift) between Θ_n and Θ_{n+1} under the null and alternative hypotheses is then given by

$$\mu_X = \begin{cases} \frac{\delta^2}{4\sigma^2} \quad , & H = 0 \\ -\frac{\delta^2}{4\sigma^2} \quad , & H = 1 \end{cases} \quad , \quad (7) \quad 20$$

and its variance is,

$$\sigma_X^2 = \frac{\delta^2}{2\sigma^2} \quad . \quad (8) \quad 22$$

The right (R) and left (L) additive factors for Θ_n in the binomial lattice can then be modeled as $\pm\sigma_X$, respectively, and their physical probabilities as,

$$p_R = 1 - p_L = \frac{\mu_X - L}{R - L} \quad . \quad (9) \quad 25$$

These factors represent clinical evidence of the drug's efficacy. Adding L for each leftward step and R for each rightward step to Θ_n models a possible evolution of the summary statistic of the clinical trial as observations get collected.⁵

Similarly, if we model the market risk process (S_n) as geometric Brownian motion, the up (U) and down (D) multiplicative factors in the binomial lattice are given by $e^{\pm s\sqrt{\Delta t}}$, respectively, where s is the underlying market risk volatility. Their physical probabilities are then given by

$$p_U = 1 - p_D = \frac{e^{r\Delta t} - D}{U - D} \quad , \quad (10) \quad 31$$

where r is the underlying cost of capital, and their risk-neutral probabilities are given by

$$q_U = 1 - q_D = \frac{e^{r_f\Delta t} - D}{U - D} \quad , \quad (11) \quad 33$$

where r_f is the risk-free rate. Here, U and D represent changes to the economic potential of the drug (e.g., the present value of its future profits, assuming trial success) due to external shocks in market conditions. The binomial lattice is then formed by multiplying S_n by U for each upward step, and by D for each downward step, which captures the evolution of market conditions over the course of the trial. For simplicity, we have assumed a uniform time between collected observations, Δt , which represents the sequential enrollment of patients into a trial. Without loss of generality, the observations could also be collected and analyzed in batches.

⁵ Note that while we have considered normally distributed response variables for expositional purposes, as long as the observations are conditionally independent and identically distributed, the log-likelihood function will follow a random walk.

Table 1
Parameter assumptions for the phase 2 and phase 3 clinical trials.

Parameter	Phase 2	Phase 3	Comments
Significance level (α)	5%	2.5%	Probability of a false approval under $H = 0$.
Statistical power ($1 - \beta$)	80%	90%	Probability of a correct approval under $H = 1$.
Standardized difference (δ/σ)	0.3	0.2	Average treatment effect under $H = 1$ in units of standard deviations of the response variable.
Target accrual ($2N$)	276	1052	Total number of patients in the trial (i.e., both arms) if run to completion. Calibrated to ensure the test is adequately powered.
Cost per patient ($K/2$)	\$40,000	\$42,000	The cost of clinical trials varies across disease groups and depends on multiple factors. On average, clinical trials have been estimated to cost \$40,000 and \$42,000 per patient for phase 2 and phase 3 trials, respectively (Battelle Technology Partnership Practice, 2015).
Trial length (T)	2 years	3 years	T/N defines the time between 2 observations, Δt , assuming uniform patient accrual.
Median annual sales	–	\$300MM	The drug is expected to generate \$300 million per year in sales if it meets its primary endpoint, and \$0 otherwise. The profits from these sales fluctuate with the market risk and are used to calculate $f(\Theta_N, S_N)$ in (3).
Net margin	–	20%	Percentage of revenues remaining as profit after all operating, interest, and tax expenses have been deducted from annual sales. In this case, the expected annual profit is \$60 MM per year.
Years of exclusivity	–	13	Revenues from a successful therapy are expected to be generated for a 13-year period of exclusivity after FDA approval before patent expiration.
Launch costs	–	\$50MM	Launch-related investment during the year a new therapy enters the market. For phase 3, this value is I in (3).
Probability of success	58.3%	59.0%	Average estimates for the probability of a successful transition from phase 2 to phase 3, and phase 3 to approval across therapeutic areas (Wong et al., 2019; Project ALPHA, 2020). These values are used to estimate the <i>a priori</i> probability of $H = 1$.
Annual market volatility (s)	50%	50%	Market risk that affects the drug's economic potential independent of its clinical trial results (i.e., scientific risk). Factors include business- and credit-cycle risk, regulation, and competition. This volatility is used to calculate the multiplicative factors U and D in the binomial lattice.
Annualized cost of capital (r)	20%	10%	Conventional estimates for early and late-stage clinical trials.
Risk-free rate (r_f)	3%	3%	Annual yield on a US 10-year Treasury Note.

1 4. Optimal decision boundaries for futility

2 Using the risk processes defined in the previous section, we can design an optimal decision boundary that, when
3 crossed, informs the sponsor that the trial should be stopped early for futility. Setting $H = 1$ in (7), we can determine
4 which nodes, (Θ_n, S_n) , result in the project being abandoned in (3). This design choice mitigates the chance of a false
5 rejection when the drug is effective, yet preserves its ability to stop early when the drug is ineffective ($H = 0$).

6 The decision boundary formed by this methodology can be illustrated using a numerical example. We consider a
7 balanced two-arm RCT that uses the z -statistic, Z_N in (4), where N is the total number of patients to be enrolled in each
8 arm of the study, as a measure of its primary quantitative endpoint. Traditionally, Z_N is compared to a critical value, λ , and
9 the drug is cleared to progress to the next phase of development (e.g., from phase 2 to phase 3) if $Z_N > \lambda$. The probability
10 of approving a therapy given a treatment effect δ is therefore $\Phi(\delta\sqrt{I_N} - \lambda)$, where $\Phi(\cdot)$ is the standard normal cumulative
11 distribution function. Here, we assume $\lambda = 1.64$ for phase 2 and $\lambda = 1.96$ for phase 3, such that the probability of a
12 false approval given the drug has no effect is 5% and 2.5%, respectively. A complete list of assumptions for this numerical
13 example are provided in Table 1.

14 To visualize the early-stopping boundary defined by applying our valuation technique, note that the interim value of
15 the z -statistic, Z_n , is related to Θ_n by the following equation

$$16 \quad Z_n = \frac{\delta\sqrt{I_n}}{2} - \frac{\Theta_n}{\delta\sqrt{I_n}}. \quad (12)$$

17 This decision boundary is depicted in Fig. 3 as a function of the number of patients, $2n$ (i.e., patients in both arms), enrolled
18 and treated in this trial. Initially, when the number of observations is small, the decision boundary is very conservative.
19 Common sense tells us that it is valuable to continue collecting data in this scenario because the small sample size limits
20 the quality of decision that can be made. Only if the drug has clearly underperformed does it make economic sense to
21 stop the trial for futility at this early stage. As the number of observations increases, the decision boundary becomes less
22 conservative because a drug that has performed poorly up to this point will have little chance of meeting its primary
23 endpoint. Finally, as the total number of patients enrolled approaches its target accrual ($2N$) of 276 patients for phase 2
24 and 1052 patients for phase 3, the decision boundary approaches $Z_n = 1.64$ and $Z_n = 1.96$, respectively, in accordance
25 with the approval criteria.

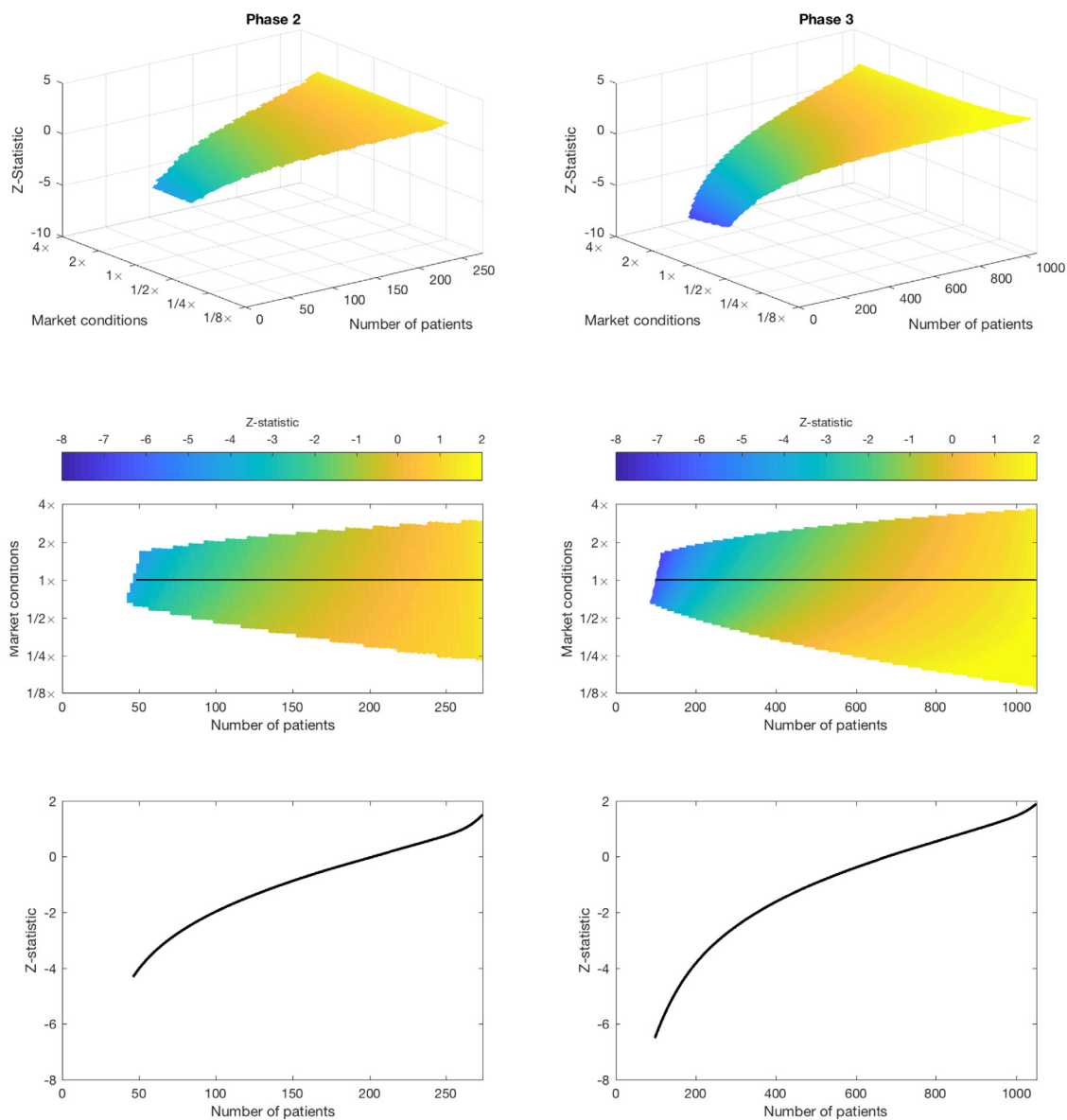


Fig. 3. Financially-optimal futility boundaries. The left and right columns show the decision boundaries for the phase 2 and phase 3 clinical trials described by Table 1. The top row provides a three-dimensional visualization of the decision boundary surface as a function of the market conditions and number of patients accrued to the study. The middle rows provide a top-down perspective of the decision boundary surface, and the bottom rows provide a cross-section of the surface given stable market conditions.

The second factor that affects the decision boundary over time is unanticipated shocks, either positive or negative, in economic conditions as modeled by the market volatility parameter. If market conditions deteriorate, continuation of the trial at earlier stages becomes less valuable. In this scenario, the optimal decision is to use a less conservative threshold for futility, which results in abandoning the trial at an earlier stage. On the other hand, if market conditions improve, then the drug becomes more valuable, and the optimal decision is to collect more evidence before we can reject the hypothesis that the drug is effective.

5. Empirical analysis

The financial value of these boundaries can be demonstrated by calibrating the parameters of our model to clinical trial designs typically used in common disease areas. In this section, we vary the cost per patient, median annual sales, and probability of a successful phase 3 trial to determine the optimal futility boundaries across disease groups. Table 2

Table 2

Phase 2 and phase 3 clinical trial statistics for selected disease areas. Abbreviations: POS_{3,APP}, probability of successful transition from phase 3 to approval; NPV, net present value; 2N, total number of patients in the trial; M, thousands; MM, millions; SD, standard deviation. Cost per patient estimates are from [Battelle Technology Partnership Practice \(2015\)](#), POS_{3,APP} estimates are from [Wong et al. \(2019\)](#) where we have used the overall success rates for hematologic and respiratory diseases, and annual sales estimates are from [Bogdan and Villiger \(2010\)](#).

Phase 2			Non-adaptive				Adaptive					
Disease	Cost per patient (\$M)	POS _{3,APP} (%)	$H = 0$		$H = 1$		$H = 0$			$H = 1$		
			NPV (\$MM)	NPV (\$MM)	2N	T	NPV (\$MM)	E[2N] (SD)	E[T] (SD)	NPV (\$MM)	E[2N] (SD)	E[T] (SD)
Cardiovascular	25.0	62.2	-6.0	22.3	276	2	-3.4	181.0 (59.6)	1.31 (0.43)	22.4	268.7 (25.7)	1.95 (0.19)
Central Nervous System	39.5	51.1	-8.3	88.8	276	2	-5.0	197.4 (51.6)	1.43 (0.37)	89.0	270.8 (18.3)	1.96 (0.13)
Metabolic	18.5	51.6	-2.7	89.8	276	2	-1.4	207.2 (46.2)	1.50 (0.34)	89.9	271.8 (14.7)	1.97 (0.11)
Hematology	30.0	59.0	-6.2	70.9	276	2	-3.7	198.1 (51.2)	1.44 (0.37)	71.1	270.9 (18.0)	1.96 (0.13)
Infectious	17.5	75.3	-2.5	89.1	276	2	-1.2	207.8 (45.9)	1.51 (0.33)	89.1	271.8 (14.5)	1.97 (0.11)
Oncology	67.5	35.5	-17.2	19.2	276	2	-7.9	154.3 (70.9)	1.12 (0.51)	20.1	262.9 (42.6)	1.91 (0.31)
Respiratory	30.5	59.0	-7.0	39.7	276	2	-4.2	188.4 (56.1)	1.37 (0.41)	39.9	269.7 (22.1)	1.95 (0.16)

Phase 3			Non-adaptive				Adaptive					
Disease	Cost per patient (\$M)	Annual sales (\$MM)	$H = 0$		$H = 1$		$H = 0$			$H = 1$		
			NPV (\$MM)	NPV (\$MM)	2N	T	NPV (\$MM)	E[2N] (SD)	E[T] (SD)	NPV (\$MM)	E[2N] (SD)	E[T] (SD)
Cardiovascular	26.0	145	-25.6	83.2	1052	3	-12.6	569.0 (211.0)	1.62 (0.60)	84.8	996.0 (148.1)	2.84 (0.42)
Central Nervous System	40.5	422	-38.3	343.5	1052	3	-22.9	682.3 (190.1)	1.95 (0.54)	344.2	1036.3 (67.0)	2.96 (0.19)
Metabolic	19.0	371	-17.0	314.1	1052	3	-10.5	717.2 (176.2)	2.05 (0.50)	314.3	1038.9 (55.3)	2.96 (0.16)
Hematology	31.0	302	-29.6	233.1	1052	3	-17.2	663.9 (193.1)	1.89 (0.55)	233.8	1031.2 (79.4)	2.94 (0.23)
Infectious	18.0	265	-16.8	209.3	1052	3	-10.1	686.6 (183.8)	1.96 (0.52)	209.7	1032.8 (71.5)	2.95 (0.20)
Oncology	69.0	344	-67.5	236.8	1052	3	-35.7	608.8 (212.3)	1.74 (0.61)	238.9	1023.7 (106.3)	2.92 (0.30)
Respiratory	31.0	213	-30.2	144.7	1052	3	-16.2	616.3 (203.9)	1.76 (0.58)	145.8	1017.9 (110.2)	2.90 (0.31)

1 reports the present values of a candidate drug for each disease group under both the null ($H = 0$) and alternative ($H = 1$)
2 hypotheses for clinical trials with (adaptive) and without (non-adaptive) the option to end the trial early for futility.

3 These table entries show that disease groups with greater costs per patient ([Battelle Technology Partnership Practice,](#)
4 [2015](#)), lower median sales ([Bogdan and Villiger, 2010](#)), and lower *a priori* probabilities of success ([Wong et al., 2019](#)) have
5 relatively less conservative decision boundaries. When a drug is ineffective, this results in greater savings in terms of total
6 expenditures, number of patients, and trial length. Here, managerial flexibility allows the sponsor to avoid significant
7 clinical trial costs when the economic potential of the drug is learned to be poor. For example, under the null hypothesis,
8 phase 3 clinical trials for oncology, which have the highest cost per patient, were stopped early by approximately 42.1%
9 on average (1.74 versus 3 years), increasing the NPV for this scenario from $-\$67.5$ million to $-\$35.7$ million. In general,
10 the average increase in NPV from using the futility boundaries was $\$3.3$ million for phase 2, and $\$14.3$ million for phase
11 3. Moreover, trials that used the optimal futility boundaries were, on average, 31% smaller in terms of total number of
12 patients and overall trial length. [Fig. 4](#) illustrates these savings by phase and disease area.

13 On the other hand, if the drug is effective, the likelihood of crossing the early-stopping boundary decreases, and so the
14 option to abandon the trial early for futility is not exercised. In this case, the option expires worthless, but at no extra cost
15 to the sponsor, causing the NPV for both the adaptive and non-adaptive trial designs to converge. The option to abandon
16 early therefore allows the sponsor to hedge the risk of downside scenarios, while maintaining their ability to fully extract
17 the benefits of positive outcomes. It is this nonlinear payoff structure that makes this adaptive design so valuable.

18 The previous analysis assumed that the cost of capital for both trials with and without the option to end the trial
19 early for futility were the same. However, as described by [Myers and Howe \(1997\)](#) and [Thakor et al. \(2017\)](#), because of
20 financial leverage, maintaining a large, fixed commitment to biopharmaceutical R&D is difficult in the face of business-
21 and credit-cycle downturns. By providing sponsors and investors with more frequent and systematic “exit options” to

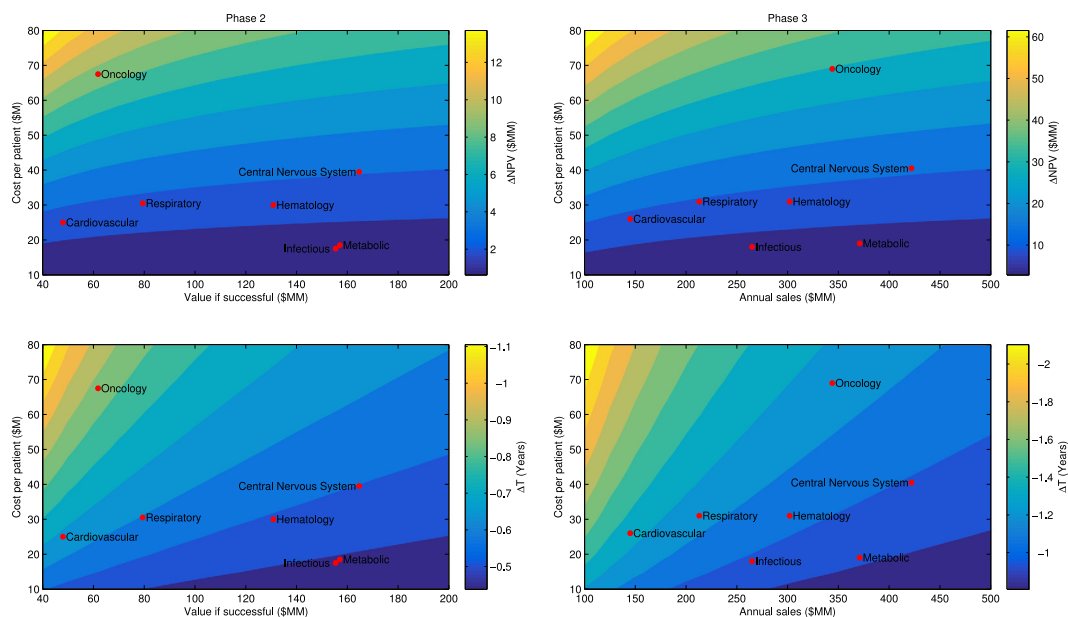


Fig. 4. Increases in value (ΔNPV) and decreases in clinical trial length (ΔT) from using the optimal futility boundaries in the case of an ineffective drug ($H = 0$).

cut their losses in the face of a market downturn, the systematic risk component of their investment will be reduced. Moreover, these adaptive clinical trials can be funded according to more detailed milestones, reducing the amount of financial leverage inherent in the project. Since biotechnology firms have greater clinical trial costs relative to their size, a reduction in the leverage effect should be more beneficial for them, thus reducing their exposure to systematic risk (i.e., their market betas) and, consequently, their cost of capital.

Fig. 5 provides a sensitivity analysis that investigates the effect of a change in the cost of capital. We find that if the cost of capital of an early-phase trial were reduced by half, from 20% per year to 10% per year (similar to the cost of capital of late-stage trials), then the value of an effective therapy increases, on average, by \$15.2 million. Similarly, a 5 percentage-point-per-year reduction in the cost of capital from 10% to 5% increases the average value of a phase 3 clinical trial under $H = 1$ by \$152.8 million. Moreover, the added value is most prominent for disease groups that have the greatest economic potential given a successful therapy. This acute sensitivity suggests that even modest reductions in the systematic risk component faced by investors can have substantial benefits in terms of larger clinical trial valuations and increased funding for biomedical R&D.

6. Discussion

Our empirical results show that fixed-sample RCTs without the option to abandon early fail to maximize the economic value of candidate drug therapies. Often, this is because of missed opportunities to stop the trial early when clinical evidence suggests lackluster future market prospects. In contrast, adaptive clinical trials that take advantage of this optionality mitigate downside risk and result in an overall increase in value to the sponsor and investors.

The framework that we have described is a simplified version of reality. The resolution of a drug's economic potential depends on multiple factors including the trajectory of disease incidence that the drug is intended to treat, the rate of population growth over time, income growth, reimbursement rates, and so forth. For example, imagine that a competing drug shows outstanding clinical results, reducing our forecasted sales. After reevaluating the project, we may decide to abandon the drug because it is no longer profitable. In our empirical results, these factors have been modeled as a general Brownian motion process, but to estimate a more accurate value of a project, we should model these other factors that affect the market risk process directly. Moreover, we could expand the leaves of the binomial pricing model's tree to include a wider range of economic potential at launch, perhaps with a blockbuster scenario in addition to other, more refined, intermediate outcomes that may not follow a log-normal distribution. In general, clinical trials can also involve complicated fee structures with various kinds of triggers for contract clauses. Moreover, the marginal cost of including an additional patient to a trial will be less than the average cost per patient because of high upfront costs. Therefore, our state-space representation can take on many forms, since each trial has its own peculiarities and unique scenarios. Therefore, using more sophisticated methods of estimating and forecasting clinical trial parameters—including forward-looking machine-learning predictions of probabilities of success, conditioned on the current state vector (Lo et al., 2019)—may add considerable value.

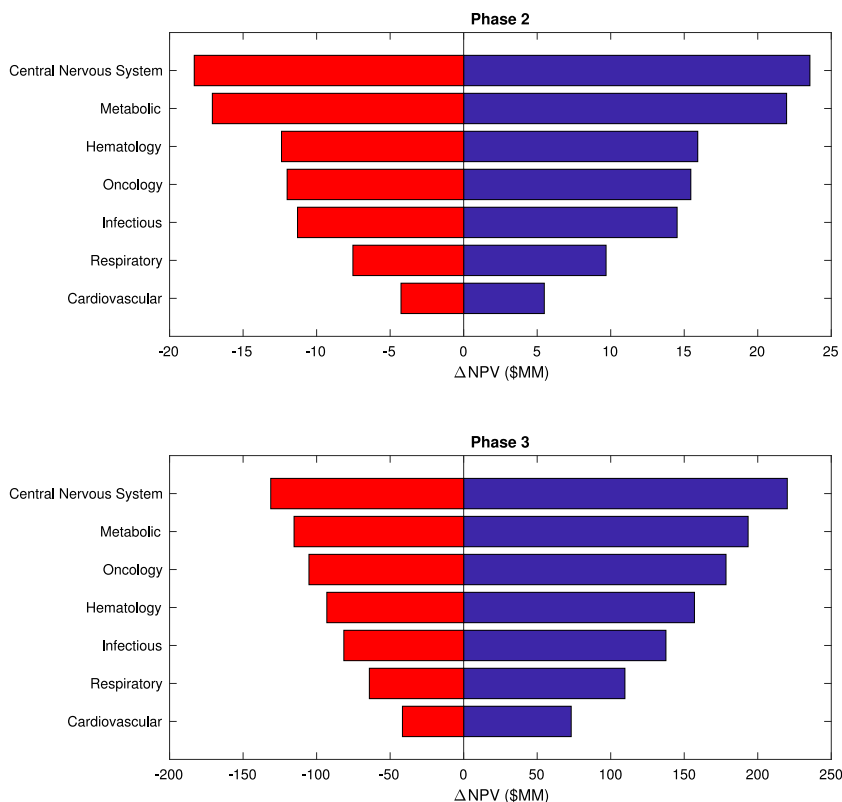


Fig. 5. Sensitivity of the value (ΔNPV) of an effective drug ($H = 1$) to the cost of capital for selected disease areas. From the left to right of each bar, the three number summary corresponds to [1.5, 1, 0.5] times the cost of capital proposed in Table 1.

1 Since R&D programs and clinical trials are complex and uncertain, modeling them can quickly become unmanageable.
 2 If we are not careful, however, the added complexity can convolute our analysis to the point where they are no longer
 3 useful to guide decision-making. Therefore, models must be pruned to the point where they show us the most important
 4 links between present and future decisions. Our primary goal in this paper was not to develop a detailed representation
 5 of the regulatory approval process, but rather to demonstrate how a clinical trial with both scientific and market risk
 6 can be valued as a sequence of real options. Nevertheless, while we have focused on a binomial recombining lattice
 7 representation, the principles behind our valuation technique can easily be extended to more general distributions that
 8 provide more realistic assumptions about the nature of the uncertainty. In these cases, simulations and sophisticated
 9 numerical analysis will be required to estimate early-stopping decision boundaries.

10 7. Conclusion

11 Clinical trials with financially-optimal futility boundaries exhibit clear economic advantages over their fixed-sample,
 12 non-adaptive counterparts. In particular, the traditional fixed-sample trials are inflexible, resulting in missed opportunities
 13 to stop the trial early for futility. Conversely, financially adaptive trials add economic value by conditionally funding future
 14 stages of a trial only when a drug shows commercial potential. The ability of our framework to systematically design
 15 decision boundaries that inform the sponsor when to stop a trial early for futility make it a potentially valuable tool for
 16 capital budgeting. While our framework can be generalized, we emphasize that careful consideration must be applied to
 17 the assumptions underlying the specific models in order to produce useful recommendations.

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References

- Banerjee, A., 2003. Real option valuation of a pharmaceutical company. *Vikalpa* 28 (2), 61–73. 2
- Battelle Technology Partnership Practice, 2015. Biopharmaceutical industry-sponsored clinical trials: Impact on state economies. <http://pharma-docs.phrma.org/sites/default/files/pdf/biopharmaceutical-industry-sponsored-clinical-trials-impact-on-state-economies.pdf>. (Accessed 25 January 2018). 3
- Berry, D.A., 1985. Interim analysis in clinical trials: Classical vs. Bayesian approaches. *Stat. Med.* 4 (4), 521–526. 4
- Berry, D.A., 1987. Interim analysis in clinical trials: The role of likelihood principle. *Amer. Statist.* 41 (2), 117–122. 5
- Berry, D.A., 1993. A case for Bayesianism in clinical trials. *Stat. Med.* 12 (15–16), 1377–1393. 6
- Berry, D.A., 2006. Bayesian clinical trials. *Nat. Rev. Drug Discov.* 5 (1), 27–36. 7
- Black, F., Scholes, M., 1973. The pricing of options and corporate liabilities. *J. Polit. Economy* 81 (3), 637–654. 8
- Bogdan, B., Villiger, R., 2010. *Valuation in Life Sciences*. Springer, Heidelberg, Germany. 9
- Brennan, M.J., Schwartz, E.S., 1985. Evaluating natural resource investments. *J. Bus.* 58 (2), 135–157. 10
- Cox, J.C., Ross, S.A., Rubinstein, M., 1979. Option pricing: a simplified approach. *J. Financ. Econ.* 7 (3), 229–264. 11
- Duffie, D., 2010. *Dynamic Asset Pricing Theory*, third ed. Princeton University Press, Princeton, NJ. 12
- Gallager, R., 2014. *Stochastic Processes: Theory for Applications*. Cambridge University Press, Cambridge, UK. 13
- Gunther McGrath, R., Nerkar, A., 2004. Real options reasoning and a new look at the R&D investment strategies of pharmaceutical firms. *Strateg. Manage. J.* 25 (1), 1–21. 14
- Harmann, M., Hassan, A., 2006. Application of real options analysis for pharmaceutical R&D project valuation—Empirical results from a survey. *Res. Policy* 35, 343–354. 15
- Hsu, J.C., Schwartz, E.S., 2008. A model of R&D valuation and the design of research incentives. *Insurance Math. Econom.* 43 (3), 350–367. 16
- Ingersoll, Jr., J.E., Ross, S.A., 1992. Waiting to invest: Investment and uncertainty. *J. Bus.* 65 (1), 1–29. 17
- Jennison, C., Turnbull, B., 1999. *Group Sequential Methods with Applications to Clinical Trials*. Chapman and Hall/CRC, Boca Raton, FL. 18
- Kellogg, D., Charnes, J.M., 2000. Real-options valuation for a biotechnology company. *Financ. Anal. J.* 56 (3), 76–84. 19
- Lo, A.W., Naraharisetti, S.V., 2014. New financing methods in the biopharma industry: A case study of Royalty Pharma, Inc. *J. Invest. Manage.* 12 (1), 4–19. 20
- Lo, A.W., Siah, K.W., Wong, C.H., 2019. Machine learning with statistical imputation for predicting drug approvals. *Harvard Data Sci. Rev.* 1 (1), 30–51. 21
- Lynch, J., Shockley, R., 2016. Valuation of a developmental drug as a real option. *J. Appl. Corp. Finance* 28 (3), 118–126. 22
- McDonald, R.L., Siegel, D.R., 1985. Investment and the valuation of firms when there is an option to shut down. *Internat. Econom. Rev.* 26 (2), 331–349. 23
- Merton, R.C., 1973. Theory of rational option pricing. *Bell J. Econ. Manage. Sci.* 4 (1), 141–183. 24
- Moel, A., Tufano, P., 2002. When are real options exercised? An empirical study of mine closings. *Rev. Financ. Stud.* 15 (1), 35–64. 25
- Myers, S.C., 1977. Determinants of corporate borrowing. *J. Financ. Econ.* 5 (2), 147–175. 26
- Myers, S.C., Howe, C.D., 1997. A life-cycle financial model of pharmaceutical R&D, working paper. Program on the Pharmaceutical Industry, Sloan School of Management, Massachusetts Institute of Technology, Cambridge, MA. 27
- Pindyck, R.S., 1993. Investments of uncertain cost. *J. Financ. Econ.* 34 (1), 53–76. 28
- Project ALPHA, 2020. Analytics for life sciences professionals and healthcare advocates: estimates of clinical trial probabilities of success. <https://projectalpha.mit.edu/pos/>. (Accessed 11 November 2020). 29
- Schwartz, E.S., 2004. Patents and R&D as real options. *Econ. Notes* 33 (1), 23–54. 30
- Sharpe, W.F., 1978. *Investments*. Prentice-Hall, New York, NY. 31
- Thakor, R.T., Anaya, N., Zhang, Y., Vilanilam, C., Siah, K.W., Wong, C.H., Lo, A.W., 2017. Just how good an investment is the biopharmaceutical sector? *Nature Biotechnol.* 35 (12), 1149. 32
- Titman, S., 1985. Urban land prices under uncertainty. *Amer. Econ. Rev.* 75 (3), 505–514. 33
- Trigeorgis, L., Mason, S.P., 1987. Valuing managerial flexibility. *Midland Corp. Finance J.* 5 (1), 14–21. 34
- Vasseur, J.P., Pérez, C.C., 2016. Pharmaceutical patents valuation through real options: Certainty equivalents and utility function. *Contaduría y Administración* 61 (4), 794–814. 35
- Wong, C.H., Siah, K.W., Lo, A.W., 2019. Estimation of clinical trial success rates and related parameters. *Biostatistics* 20 (2), 273–286. 36