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A novel valuation model for medical intervention development based on progressive dynamic changes that integrates Health Technology Assessment outcomes with early-stage innovation and indication-specific clinical success rates

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Abstract

All stakeholders involved in the development, licencing, and market access of health care technologies use stage-specific valuation matched that integrates risks and outcomes to inform their decision making.

A stage-specific valuation method, based on defining future cash flows for a product that are success-rate probability adjusted prior to being discounted with a risk rate, is termed risk-adjusted net present value, and a negative value indicates that a loss will be made and therefore the product should probably not be developed. However, values exited from these calculations can be highly variable depending on the data used to generate the calculation, and in light of the estimated $2.6bn in capitalised costs that is necessary to move an innovation to market, without any guarantee of product reimbursement, the financial risk is very high. Indeed recent return on investment numbers for life science investment are staggeringly low, significantly lower than the weight-adjusted cost of capital, implying healthcare R&D is economically unattractive. The outcome is that the objectives of modern intervention R&D are more linked to moving risk off the books or downstream to larger companies, which at face value seem better positioned to develop the products further, when in fact a complete reconfiguration of approaches, models and realistic actions and strategies are likely to generate more value.

As NPV calculations are only as good as the data used to generate it, and both accurate and comprehensive values ideally should be used, based on real market dynamic, the latest clinical success rates and considering the latest reimbursement approaches, more formal HTAs for therapeutic intervention, we reassessed valuation approaches, integrated the reality of later stage clinical validation, product reimbursement based on Health Technology Assessment perspectives, and downstream costs to generate a whole value chain calculation. The outcomes led us to consider an alternative risk rate model based on dynamic changes that occur throughout the R&D process. While modelled for medical intervention development, the outcomes of this work can also be applied for evaluation of diagnostics and

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medical devices.
Using four intervention types in two diverse indications as a model, we simulated various valuations, and our analyses suggest that using indication-specific success rates provides a more accurate value determination, and that a different risk rate approach should be followed, which was further validated using real market data. The implication is that all stakeholders need to take a holistic approach to valuation and working together for mutual benefit to de-risk development programmes and pipelines. This will enable all of them to use the same values before and throughout the R&D process, and facilitate better decision making, clearer trust as the innovation changes hands up the value chain, and eventually better and more cost-effective therapies.

Keywords: Innovation management, Valuation modelling, Full economic cost, Inverse modelling, Alternative risk rates

Introduction

For any entrepreneurial venture, a positive net present value (rNPV) calculation on any product in development is a good indication that upon market release, the financial return will exceed the cumulative life cycle costs of research, development, market validation, market access, market release, manufacture and sales and therefore potentially justify the initial outlay; this summarised as return on investment (ROI). In healthcare and particularly therapeutic intervention development, this life cycle is long (FDA, 2016; Stewart, Allison, & Johnson, 2018), typically over 14 years, and expensive ($2.6bn, (DiMasi, Grabowski, & Hansen, 2016)) which means that significant risk has to be carried for a long duration before knowing if the product was worth the investment. The high costs of development are not only linked to the out of pocket costs but also the opportunistic costs of capital, in that if a decision was made to perform an alternative innovative investment what return could be generated with that money. The ROI, therefore, on any investment, should at a minimum be 1, and equivalent to the Weight adjusted cost of capital (WACC, indicated as a percentage, and represents the minimum return that should occur on an investment, if nothing more was done by the entity than invest in bonds, and bank interest).

This significant risk has led to the establishment and now standard usage of a risk-adjusted NPV, abbreviated to rNPV (Villiger, 2011; Booth, 2011; Booth, 2014; Dillon, 2015; Drummond, 2013) for life science investments, in which the risk rate is typically the company-specific internal rate of return (IRR) (Gallo, 2016).

At present, the ROI on pharmaceutical R&D is reported to be dropping below an estimated 2% for 2018 (in 2017 in was 3.2%, (Terry & Lesser, 2017)), while the weight-adjusted cost of capital is presently at an industry average of 8.13% (Stern communication, 2017). This means that to perform research and development not only carries significant financial risk but also fundamentally diminishes the value of the money being engaged. Despite this market reality, rNPVs on projects and portfolios at the start-up stage for healthcare-focused endeavours are communicated either publicly or privately that greatly exceed what is actually happening in the marketplace, which suggests that the data being used in rNPV calculations may be incorrect, and there is a disconnect

between stakeholders, that has serious ramifications for when an early stage company attempts to outlicence its innovation to a larger player.

There are several possible sources of this problem: the first is the definition of the terminal market value in the rNPV equation, in which global or Total Accessible Market (TAM) values are used, yet launching a healthcare innovation in different 'regulatory' trading blocks (North America, Europe, Asia-Pacific, Mercosur, and potential further geographic distinctions) cannot occur without satisfying the local clinical requirements which cannot be geographically transferred (Shenoy, 2016, Ndebele P et al 2014, Van Norman, 2016, Dunlop et al., 2016, Allen, Liberti, Walker, & Salek, 2017, Angelis, Lange, & Kanavos, 2018); the second is the pertinence of the Health Technology Assessment (HTA) dossier which includes Cost-effectiveness analyses comparing the new intervention to existing standards of care to define where and at what price the intervention will be reimbursed and that while valuations simplify global market values, the geographic diversity of HTA and if, how and for what decisions are made means local geography valuations have to be integrated; the third is the complexity and volume of clinical data that needs to be generated, managed and continually collected to generate a high-quality reimbursement argument with associated costs; the fourth is the indication specific probability of clinical transition of a therapeutic; and the fifth is the perception that total indicated sales represents the terminal market value to be used, ignoring the reality that nearly two thirds of the sales costs are used to manufacture and sell the final product.

Literature review

The understood fallibilities of rNPV calculations has led to the development of new valuation models, such as the Headroom method that determines the maximum reimbursable price (Cosh, Girling, & Lilford, 2007; Girling, Lilford, Cole, & Young, 2015; Markiewicz, van Til, & IJzerman, 2016), Early-Stage Health Economic models (Brandes, Sinner, Kääb, & Rogowski, 2015; Miquel-Cases, Steuten, Retèl, & van Harten, 2015; Retèl, Grutters, van Harten, & Joore, 2013) which only study interventions ready for clinical trials or market launch, or Multi-Criteria Decision Analysis (Middelkamp, van der Meer, Hummel, et al., 2016; Thokala, Devlin, Marsh, et al., 2016) which is based on collecting feedback from stakeholders based on hypothetical products and then use this to estimate the value of the product. The maximum reimbursable price and early-stage health economic models seem best suited when a product is already on the market for one disease, and drug repositioning is being considered as a way to increase revenues, without high development cost and risk. Arguably, this is an extensively abbreviated rNPV calculation, in which late stage clinical trial costs, and scaled up manufacturing and sales are used as cost values; which serves as good paradigm when the product is launched. For earlier stage considerations however and accounting for the perspective of either start-up companies or early-stage R&D in larger companies, the calculation does not include previous risks and costs.

Regarding costing, there have been many studies performed since 1979 on the costs of bringing a drug to market (these studies have been neatly summarised in Mestre-Ferrandiz, Sussex, & Towse, 2012), however the costing indicated in each referenced study did not include current clinical data requirements of review and reimbursement

agencies, post-market release costs such as manufacturing, sales and general expenses, and continued clinical trials, all of which need to be paid for from the drug revenues.

The issue has not been helped by the general perspective in the industry that valuations are unreliable (Dillon, 2015). However, when analysing what numbers are inputted into the rNPV calculations, the industry perspective becomes unsurprising, despite NPV estimations being logical. As Svennebring and Wikberg (2013) reported, "Mathematical models are fabrications designed to capture the most essential aspects of reality. It is therefore imperative to acknowledge all imperfections to the models and to the degree it is possible to account for them in the process of setting the parameters (i.e. parameter estimates) fed to the model or to craft the models."

In recent years, several teams have reassessed the NPV estimation models: Svennebring and Wikberg (2013) proposed extensions to the existing model that included constant probability rates of finding a drug candidate, a dynamic probability tree for cumulative identification of new candidates and that more than one compound can be selected for clinical development. Real option-based valuations (Perlitz et al 2002) have also been proposed which are founded more in managerial flexibility and strategic value, while an effectuation model (Ahn, York, Wu, Suharto, & Daim, 2015) which integrates means, loss, partnerships and expecting the unexpected can be used to identify value differences between pipelines.

However, there are still several underlying issues pertinent to generating an effective valuation: Zizlavsky (2014) highlighted that one of the fundamental problems in NPV approaches is that average probabilities of success or occurrence occur, when in reality, indication-specific probabilities should be used. While Fountain (2017) indicated that: "A large portion of a biotechnology company's value is derived from its R&D assets, discounted cash flow valuation (or DCF) proves to be a more effective valuation technique. However, this method is extremely sensitive to inputs related to future riskiness and returns of the company. So, wrong inputs can lead DCF in returning erroneous company values. The problem is, of course, discounting for risk."

While many authors (Rottgen, 2018, Stewart et al 2001) have indicated that failure to include the total costs in their calculations can result in incorrect estimates. Fundamentally, the issue is that full economic costing of development is not used in early-stage value calculations. A risk-profiled NPV model (rpNPV) did attempt to integrate in more market-related variables (Walker, Turner, & Johnson, r., 2015); this was the closest model that attempted to integrate full economic costs. However, the model was using generic rather than indication-specific variables, such as very long clinical trial phases, and did not consider SAM and SOM (serviceable accessible market [SAM] (geography differentiated market value) and serviceable obtainable market [SOM] (percent of market penetrance that can be achieved within a serviceable accessible market), as a function of terminal market value related to existing standards of care upon which decisions to reimburse are made. These are additional but critical variables that need to be integrated into the valuation to assess if the innovation to be developed has the potential to have a positive rNPV.

From our experience, many small to medium companies in the field still have incomplete perspectives of the full market chain and pharma marketplace, especially in the link between regulatory approval and reimbursement and what the priorities of larger entities are. The general understanding is that the two are synonymous, when in reality,

they are not. Petersdorf and Kanavos (2015) succinctly summarised this as follows: "HTA agencies operate within a network of other healthcare actors that, together, determine whether a medicine is allowed to enter a market, who receives the medicine, and who pays for therapies. Regulator bodies such as the European Medicines Agency's (EMA) Committee for Medicinal Products for Human Use are responsible for assessing drugs on their efficacy and safety. Approval is required from these agencies to receive market authorization. National or regional bodies then negotiate with the manufacturer (or the drug wholesaler) on drug price, reimbursement status (as in specifically for what based on evidence-based medicine) and allocated funding. HTA bodies inform these three latter considerations."

There are also a lack of robust peer-reviewed publications linking pricing and reimbursement (P&R) procedures outcomes such as Health Technology Assessments (HTAs) with the development stage values of medical interventions using relative negative predictive value (rNPV) financial model valuation based methods: yet the outcomes of the P&R and HTAs define the terminal market value of the intervention which by definition directly informs the rNPV of the intervention in development at any given stage. There is an emerging use of Early Health Technology Assessment (IJzerman, Koffijberg, Fenwick, & Krahn, 2017), which defines 'Early HTA' as assessment " of medical products just before and also at the early stages of clinical use" and that the outcomes can be used to manage risk in technology portfolios and their market application.

Research question

As rNPV is the de facto valuation model used throughout the industry, while the previous studies indicated above and several recent articles in the past year reporting on updated clinical trial success and our own experiences, we wanted to investigate the impact of indication-specific success rates, the relevance of HTA determined SAM/SOM values and full economic costing on rNPV valuations in healthcare.

We perceived that the level of 'value over-optimism' of early-stage innovations, specifically those performed in start-up companies, is being misunderstood as later stage stakeholders, such as larger pharmaceutical and biopharmaceutical companies, being innovation stale, a perspective also indicated in the rpNPV model (Walker et al., 2015). However, this is contradicted by reviewing pharma and biopharmaceutical company pipelines that perform valuations that typically include all the pertinent market dynamics.

With regard to all value modelling in life science, success rate probabilities used in rNPV calculations correspond to the movement into the next phase, not the success rate of the innovation at that specific stage progressing all the way to market, yet no revenue is generated by a medical product undergoing a phase II study; if an early-stage investment decision uses these values, with the strategic aim to licence to a larger company for further development, despite traditional rNPV calculations providing positive values, the reality for the larger company is that considerable risk is still included in the innovation.

We wanted to know why this happens and also chose to reverse model how up-to-date and complete market realities based on publicly available sales revenues, when

integrated into the rNPV calculation influence early valuation calculations accounting for the various different data inputs.

This was enabled by two recent studies published in 2018 (Thomas et al., n.d.; Wong, Siah, & Lo, 2018), that has included indication-specific statistics and clinical success transition probabilities, based on the analysis of large sets of historical data, permitting us to use as detailed and up-to-date data as possible. Success rates are used for the probability adjustments in rNPV valuations (Villiger, 2011.; Booth, 2011; Booth, 2014; Dillon, 2015; Drummond, 2013), and based on our experiences from working throughout the value chain (Dando, 2017; Dando & Weiss, 2013; Larkin, Hatswell, Nathan, Lebmeier, & Lee, 2015; Salas, Hughes, Zuluaga, Vardeva, & Lebmeier, 2009) with the whole spectrum of stakeholders, we identified several key factors that needed to be integrated into the calculation, which would possibly provide more realistic indicators of value.

One key aspect was the link HTA indicated benefits and perceived terminal market values, which at present seem to be based on the total accessible market, i.e. the global market, yet HTA decisions are geographically constrained. The importance, therefore is what the values that are reported in market analyses correspond to, which are: The total sales in the precise geographic market where those sales will occur based on clinical outputs on a defined population.

Market values are typically reported by indication or specific disease application, which falls within the group of diseases linked to the indication, while total global market values are reported with percentage by geographic area. Geographic areas typically being the USA., Europe, and Asia-Pacific (APAC); however for a HTA evaluation, and a medical intervention development regulatory perspective, clinical data generated in one geographic block or free trade area, is not necessarily accepted in another, necessitating further development costs (Van Norman, 2016). Each geographic area has its own specific Health Technology Assessment requirement, with different constraints: as one example North America uses Disability Adjusted Life Years in the Cost:Benefit section of HTA, while Europe uses Quality of Life Years in the same section. This means that the intervention evaluation procedures during later stage clinical validations are regulatory different.

Given that the ROI on drug development is below the WACC, the implication is that the market-related outcomes of P&R procedures and HTAs play a critical role in defining if a health technology has any market viability. Indeed, as Villiger and Bogdan (2006) reported, “People want a drug to be valued to predict whether it will make money. However, valuation only calculates the odds. The value tells you whether it is worthwhile to risk the bet and how much you should bet, but it does not tell you whether you are going to win.”

Based on the latest industry data, identifying interventions and prioritising those for investment that address all stakeholder needs has not been done. This also raised the question if the risk values being used in the calculations are ideal, which prompted us to develop a de novo model that is presented in this article.

Methods/experimental

In performing this study, we used the industry standardised valuation model and equations for performing rNPV calculations which can be found from numerous sources (Villiger 2011., Dillon, 2015, Svennebring & Wikberg, 2013, Stewart et al., 2018). Our

research approach started by integrating Full development costs into the rNPV calculation, followed by indication-specific success rates obtained from recent analysis (Wong et al., 2018), published market size values for the complete drug development lifecycle. Differing terminal market values were based upon the level of market penetrance of existing standards of care (therapeutics) for the different conditions, against which any new intervention would be compared for reimbursement purposes. This enabled us to model stage of development specific rNPV calculations as a level of "arguable-competitiveness to existing standard of care" of the product. Further in-depth analysis can only be performed comparing original proprietary interventions being developed to the mechanisms of action and agreed reimbursement usage of the existing standards of care, which can only be calculated using clients' proprietary information.

Sensitivity analysis was performed at multiple levels: different market penetrations, generalised vs latest indication-specific success rates, and highest vs lowest potential costing (explained below).

rNPV Model validation was performed using four different possible interventions in two different indications, while real-world model validation was performed using 3 interventions presently on the market with significant revenues.

Market size

To perform this study, we chose to focus on cardiovascular and endocrinological indications, modelling both biologics and chemical entities. For cardiovascular we modelled chemical entities for hypertension and biologics for anticoagulants, while for endocrinology we modelled chemical entities for non-insulin drugs and biologics for insulin-related drugs. Information on market sizes was obtained from the following sources. Cardiovascular hypertension market info: anti Hypertension interventions (Goldstein research, 2018); Cardiovascular anticoagulants market info (Research and markets), Endocrinology insulin and non-insulin market info (Zion Market research, 2016). All

Table 1 TAM, and SAM for hypertension, blood thinning, insulin-related and non-insulin-related drugs. Figures presented are annual values

	USA	Europe	APAC
Anti-hypertension drugs TAM: $33bn			
SAM market share	40%	20%	23%
SAM value	$13.2bn	$6.6bn	$7.59bn
Anti-coagulant drugs TAM: $25bn			
SAM market share	40%	30%	24%
SAM value	$10bn	$7.5bn	$6bn
Insulin-related drugs TAM: $42bn			
SAM market share	40%	20%	30%
SAM value	$16.8bn	$8.4bn	$12.6bn
Non-insulin-related drugs TAM: $27bn			
SAM market share	38%	20%	28%
SAM value	$10.26bn	$5.4bn	$7.56bn

Total accessible market (TAM) and serviceable accessible markets (SAM) for anti-hypertension drugs, anti-coagulant drugs, insulin-related and non-insulin-related drugs. The TAM corresponds to the total global market, while the SAMs are indicated for the three major trading blocks

TAM and SAM values are indicated in Table 1. For each modelling, we elected to compare the lowest and highest markets to provide the limits of valuation calculations.

To model SOM values, we obtained information on the top ten antihypertensive drugs being sold in the United Kingdom from Statista (Statista, 2018) and converted these figures into market penetrance values, which were then used to calculate the various terminal values that should be inserted into the rNPV calculations, and are indicated in Table 2. Values ranged from 0.62 to 40% of the market share, and we modelled terminal market values ranging from 1 to 100%. The same hypothetical percent market shares were used for modelling in all other indications and interventions described.

Full development costs vs abbreviated costs (high and low versions)

For development costs, we used three different sources of information from DiMasi (DiMasi et al., 2016), Booth (B. Booth, 2011, B. Booth, 2014) or Sertkaya (Sertkaya, Birkenbach, Berlind, & Eyraud, 2014). DiMasi's estimates include the costs of failure (out of pocket costs) therefore representing the high cost threshold, although we did not include capitalisation-related costs as there is still debate on this point, and capitalisation costs are entity specific, while Sertkaya's costs represent a more critical path costing, and therefore represent the lowest cost threshold. Neither team provided information on discovery or preclinical work; therefore, we combined these peer-reviewed assessments with Booth's professional experience of discovery and preclinical costs to generate two costing models: low and high cost estimates in either an abbreviated (historically used values) or a full economic cost (FEC) value including all costs. Additionally, the preclinical development of biologics has been reported to be 1.45 times higher than for chemical entities, while clinical translation costs are similar (Mestre-Ferrandiz et al., 2012), which have also been included in the input values.

For an effective assessment of the HTA dossier, entities responsible for reimbursement perform meta-analyses and systematic reviews, in which, providing the clinical trial has been implemented correctly, the new intervention is compared to the existing standard-of-care. To be able to prove that the new intervention is comparable or better

Table 2 Real-world SOM calculations for hypertension based on 2017 top ten UK drug prescriptions for hypertension

Name	Number of pills sold	% market share of top ten (SOM)
Ramipril	27,918,000	40.47
Lisinopril	9,087,000	13.17
Losartan potassium	9,447,000	13.70
Candesartan Cilexetil	6,738,000	9.77
Doxazosin Mesilate	6,519,000	9.45
Perindopril Erbumine	4,701,000	6.81
Irbesartan	1,911,000	2.77
Enalapril Maleate	1,756,000	2.55
Olmesartan Medoxomil	474,000	0.69
Moxonidine	430,000	0.62
Total	68,981,000	100

The sales of the top ten leading antihypertension drugs in the UK were obtained from Statista, and then converted into real-world serviceable obtainable market (SOM) percentages to generate market penetrance values for future simulations

than the existing standard-of-care, for major diseases, large and well-designed phase 3 trials generating robust and meaning full data for reimbursement decision-makers are required to obtain reimbursement and market access enabling sales. As multiple trials are required, for the purpose of this work we assumed it to be 2 additional trials, and therefore multiplied the costs by 2.

To submit a reimbursement dossier without sufficient, robust and meaningful clinical evidence leads to a very high risk of not getting reimbursement, and 2 trials would be the minimum. Assessment of leading drugs on the market and their clinical validation steps, this may still be an underestimate. Successful interventions launched globally have revealed that typically more than 10 phase III clinical trials in different geographies are typically required for sufficient clinical evidence to be obtained.

There is the registration cost: the FDA published price for the review of a dossier with clinical data is around $2mn, while the equivalent EMA costs are around $600 k, and we used the average of the two values. Once the FDA, EMA (or other regulatory bodies) approves the intervention, it then passes into HTA review to see for whom and for how much it should be prescribed and then the manufacturing, post-market research and launch costs that have been estimated to be an additional $350mn for a single large economic block.

Finally, at the stage of market release, there is also the manufacturing cost of the intervention; this has two components, the facility and the actual therapeutic manufacture. Manufacturing a biologic requires a dedicated facility, costing on average $350mn, without considering running costs, while a chemical entity manufacturing facility costs on average $65mn. Actual manufacture of the pre-launch phase has been estimated to reach 30% of the costs of sales (Basu, Joglekar, Rai, Suresh, & Vernon, 2008); for the purpose of generating the most optimistic possible rNPV, we elected to use the lowest possible value for manufacturing.

The different values are indicated in Table 3 and correspond to the costs to get the drug to market launch and the first 2 years of zero to low sales. Higher downstream costs (scaled up manufacturing, continued clinical studies) for the later stages of were not included for rNPV calculations, which would have to be done on an intervention-by-intervention basis depending on the outcomes of the original clinical trials and recommendations of the reimbursing agencies.

Success rates

Success rates were obtained from DiMasi and again Booth's discovery and preclinical averages and included with DiMasi's to generate the "generic" success rates.

We used information from the latest publications (Thomas et al., n.d.; Wong et al., 2018) reported in the supplement to the article, which contains 11 years of data from 2005 to 2015, related to multiple indications and the success rate transitions from phase I to phase III of the clinical trial. We averaged all 11 years of success-rate data by phase for Cardiovascular or Endocrinological/Metabolic indications and used this as the 'success rate' for the pertinent indication.

For the latest reimbursement rate, we used NICEs 2000 to 2018 'recommended' percentage indicating no market restriction, i.e. access to the full licenced indication (NICE, 2018). The success rates used for modelling are indicated in Table 4, while Table 5 indicates the cumulative success rate of an intervention transitioning from any point on the value chain to the market for the two indications.

Table 3 Costs for full development used for modelling (numbers in millions of USD)

	DiMasi OOP-CE (high)	Sertkaya CP-CE (low)	DiMasi OOP-Bio (high)	Sertkaya CP-Bio (low)
a. Abbreviated cost estimate				
Registration	1.3	1.3	1.3	1.3
Phase III	255.4	25	255.4	25
Phase II	58.6	7	58.6	7
Phase I	25.3	2	25.3	2
Preclinical	110	7	159	10
Discovery	119	6	119	6
Total cost	569.6	48.3	618.6	51.3
b. FEC cost estimate				
Manufacturing costs	400	400	400	400
Facility costs	65	65	350	350
Launch/post-market R&D	350	350	350	350
Registration	1.3	1.3	1.3	1.3
Add. HTA CTs	510.8	50	510.8	50
Phase III	255.4	25	255.4	25
Phase II	58.6	7	58.6	7
Phase I	25.3	2	25.3	2
Preclinical	110	7	159	10
Discovery	119	6	119	6
Total	1895.4	913.3	2229.4	1201.3

a. Low cost estimates corresponding to values obtained from 3 independent sources in which costs end at the registration phase for both chemical entity and biologic-based medical interventions
b. High cost estimates corresponding to values obtained from 3 independent sources in which costs end at the registration phase for both chemical entity and biologic-based medical interventions

Calculations

rNPV calculations were performed using the above data and the accepted equation. The current industry WACC values from Stern NYC were used, along with the industry standard IRR of 8%. Any additional values such as those used in the UK model, or the real-world model is explained in the pertinent section.

Table 4 Phase success rates (%) used for modelling

	Generic	Indication-specific CVD*	Indication-specific Endo/Meta*
Registration	90	56	56
Phase III	62	62	54
Phase II	36	43	40
Phase I	59.52	46	52
Preclinical	62	62	62
Discovery	50	50	50

*Latest: combination of Wong, Siah, and Lo clinical phases and NICE registration data
Stage-specific transition success rates for medical intervention development obtained from publications by DiMasi, Sertkaya or Wong et al. Values indicate generic success rates by phase or latest indication-specific success rates by phase. The latest CVD and latest Endo/Meta correspond to the Cardiovascular and Endocrinological/Metabolic corresponds to the average of 11 years of data indicated in the supplementary material of Wong et al. (2018), with the registration rate corresponding to the UK NICE latest figures

Table 5 Indication-specific cumulative success rates

	Latest CVD (%)	Latest endo/meta (%)	Generic (%)
Registration to market	56	56	90
Phase III to market	34.72	30.24	55.80
Phase II to market	14.93	12.1	20.09
Phase I to market	6.87	6.3	11.96
Preclinical to market	4.26	3.9	7.41
Discovery to market	2.13	1.95	3.71

Cumulative success rates to market from specific stages of intervention development calculated from Table 4

Results

Modelling the rNPVs

We first set out to determine the impact on output valuations when the full economic cost (FEC) or the abbreviated cost of development were used in the SAM. Using just the USA as the SAM market example the high costs were compared to the low costs using generic success rates for four potential interventions; Biologics treatment for cardiac-related disease, biologics treatment for diabetic-linked diseases, chemical entity–based treatment for cardiac-related disease, and chemical entity–based treatment for diabetic linked diseases. as expected and indicated in Fig. 1, independent of the disease indication or application, using FEC resulted in a reduced rNPV value along the value chain. On average and independent of the clinical phase, rNPVs were $49 million dollars higher between abbreviated low costs and FEC low costs, and $71 million dollars higher between abbreviated high costs and FEC high costs. The implication being clear that whether your costs are critical path or encompassing total out of pocket, reducing costs will increase the rNPV. When comparing phase by phase, rNPVs for abbreviated costs were on average $10.5 million higher for both phases 2 and 3 compared to the FEC, while phase 1 rNPVs for abbreviated costs were $36 million higher, implying that increasing the cost effectiveness of the early stage R&D will have a greater impact on longer term value.

When we integrated into the rNPV calculations the latest indication-specific success rates, the impact was more dramatic. At the phase 2 level, using indication-specific success rates, on average a $180 million decrease in rNPV was observed, while at the phase 3 level, the average decrease was $507 million (averaging was performed across indication and therapeutic approach. The critical importance and ramifications of this are further explored in the real-world modelling.

As the FEC High and FEC Low corresponded to the total value chain costs up to the first two years of market release, and indication-specific success rates arguably provide a more accurate analysis, all subsequent simulations were performed using these values, comparing the USA and European markets.

The next simulation was to integrate into the level of local market penetrance, or SOM. In healthcare interventions, SOM is determined by the existing standard of care, the outcomes of the clinical trials and specifically the QALY or DALY outcomes, how convincing the clinical data is compared to the null hypothesis and the potential pricing. For example, generating a fifth in class (but not generic) me-too intervention and obtaining reimbursement can often entail offering significant price reductions to the

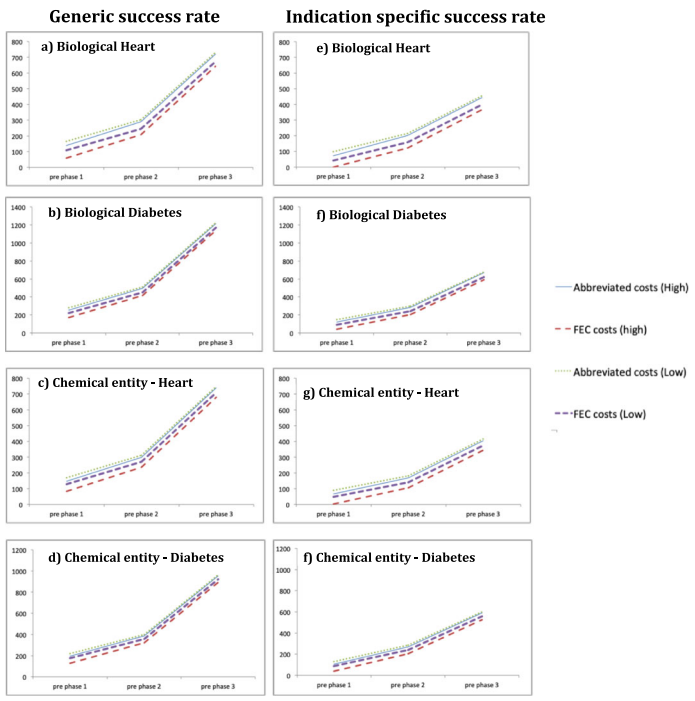


Fig. 1 Stage-specific rNPV calculations for the four modelled interventions, using generic success rates comparing abbreviated or full high and low costs, and indication-specific success rates comparing abbreviated or full high and low costs**.** rNPV calculations were made for chemical entity or biological interventions for diabetic or heart disorders using low and high versions of abbreviated or full economic costs and generic success rates (panels **a**, **b**, **c**, and **d**) and for the latest indication-specific success rates (panels **e**, **f**, **g**, and **h**)

paying body to ensure market penetrance, while the mechanism of action, off-target effects and drug-drug interactions can further influence the paying bodies willingness to consider the intervention.

Much of this forms part of pricing and reimbursement decision making through procedures like HTAs, which can therefore influence the pricing**.** HTAs are nowadays well established not only in traditional HTA markets like the United Kingdom, but also elsewhere like other European markets and in the USA, Canada, and Asia, and it is gaining further global momentum. While processes and methods may differ from one jurisdiction to others the basic principles of the data used being relevant and meaningful to decision-makers and the value proposition being robust and can be substantiated remains across jurisdictions. Therefore, we have researched these aspects and reflected them against our own experience conducting and advising on HTAs in these jurisdictions to inform our analyses presented in this article. We especially considered robustness, relevance, and meaningfulness of the underlying data as the overlapping areas for HTA decision-making in our work. For this, we considered published sources as well as our own experience. As the work we present in this article is a novel approach and has not been done before, we firmly believe this to be a robust approach to this decision analysis.

As indicated in Table 6 and taking the perspective of an early-stage company, considering moving forward one of its compounds in which alternative interventions would represent the competing products with different market shares we modelled how the estimated "market penetrance by percentage" would further influence the rNPV (It

should be noted that the 100% value indicated in these tables corresponds to the SAM value). Taking into consideration that pre-phase 1 would involve spending anything from $18 million to $250 million, it became clear that any intervention, for whatever rationale, would need to obtain greater than 15% market share to be worthwhile, with the lower market share only potentially making returns in the long term, with a potential to reposition the intervention in alternative diseases in the same indication to increase revenue. This was the same for all disease/intervention type combinations. As rNPVs are additive, for early-stage entities planning intervention development, it also raises the strategic necessity of internationalising as early as possible: while it is tempting to establish foreign subsidiaries to access markets, this can be expensive, and for an early-stage company longer term strategies of joint development and partnering will potentially create future value when a more local based perspective would not. It also addresses the importance of above regarding HTA's and reimbursement decisions taken in trading blocks such as Europe, in that one country may make a different decision to another, irrespective of the transferability of the HTA dossier and market penetrance modelling needs to be performed in some detail.

This raises some interesting points for healthcare innovation; early-stage development carries an enormous amount of cost and risk, which is not alleviated by clinical progress alone in its present model, and indeed further development occurring as part of a large pharmaceutical internal innovation programme, or in-licenced from a smaller company by a large pharmaceutical company still has high cost and risk. The most viable solution is to define a strategy that only generates best-in-class interventions that will be prescribed and paid for; however, this necessitates that payers will be prepared to pay the premium that would at least cover the development costs. Unfortunately, this has clearly not been the case; using Deloitte's figures on R&D ROI in the pharmaceutical industry from 2010 to 2015 (Terry & Lesser, 2017). We mapped these figures with the cardiovascular clinical phase success rates in the same period (Wong et al., 2018) which indicated that despite increases in phase III success i.e. that the medical intervention is working as defined by it primary and secondary endpoints, the innovations are not generating value (see Fig. 2).

However, in rNPV calculations, the success rates inputted typically correspond to the success rate of transition into the next phase, not the cumulative success rate of the intervention at that specific phase, going all the way to market. We therefore repeated the rNPV calculations this time using the indication-specific cumulative success rates.

Figure 3 illustrates that for all conditions and intervention types, using these success rates results in no rNPV value being observed before the intervention has entered phase 3 clinical trials. Using this approach, this may potentially correlate to large company strategies of not in-licencing anything that has not completed phase 2 clinical studies. This is modelled below further using real sales data, and it is possible that only using high completed phase 2 rNPVs as an indication of potential value may be misleading and an overestimate of the value. However, we consider that the pertinence of successful movement to market is not something that can be ignored.

Changing the risk rate

In light of the previous modelling, despite rNPV valuations increasing with clinical phase success and success rates increasing, if the ROI is decreasing, the implication is

Table 6 SOM rNPVs for each market using real-world data potential market share (numbers in millions of USD)

Market penetration		100%	40%	15%	10%	7%	3%	1%
a. Chemical entity-based intervention								
Heart								
High cost	Pre-phase 1	39.21	15.684	5.8815	3.921	2.7447	1.1763	0.3921
	Pre-phase 2	204.49	81.796	30.6735	20.449	14.3143	6.1347	2.0449
	Pre-phase 3	526.12	210.448	78.918	52.612	36.8284	15.7836	5.2612
USA								
Low cost	Pre-phase 1	86.9	34.76	13.035	8.69	6.083	2.607	0.869
	Pre-phase 2	240.91	96.364	36.1365	24.091	16.8637	7.2273	2.4091
	Pre-phase 3	556.84	222.736	83.526	55.684	38.9788	16.7052	5.5684
High cost	Pre-phase 1	19.6	7.84	2.94	1.96	1.372	0.588	0.196
	Pre-phase 2	102.24	40.896	15.336	10.224	7.1568	3.0672	1.0224
	Pre-phase 3	263.06	105.224	39.459	26.306	18.4142	7.8918	2.6306
Europe								
Low cost	Pre-phase 1	43.45	17.38	6.5175	4.345	3.0415	1.3035	0.4345
	Pre-phase 2	120.46	48.184	18.069	12.046	8.4322	3.6138	1.2046
	Pre-phase 3	278.42	111.368	41.763	27.842	19.4894	8.3526	2.7842
Diabetes								
High cost	Pre-phase 1	3.56	1.424	0.534	0.356	0.2492	0.1068	0.0356
	Pre-phase 2	106.94	42.776	16.041	10.694	7.4858	3.2082	1.0694
	Pre-phase 3	345.02	138.008	51.753	34.502	24.1514	10.3506	3.4502
USA								
Low cost	Pre-phase 1	48.87	19.548	7.3305	4.887	3.4209	1.4661	0.4887
	Pre-phase 2	141.54	56.616	21.231	14.154	9.9078	4.2462	1.4154
	Pre-phase 3	374.21	149.684	56.1315	37.421	26.1947	11.2263	3.7421
High cost	Pre-phase 1	1.87	0.748	0.2805	0.187	0.1309	0.0561	0.0187
	Pre-phase 2	56.28	22.512	8.442	5.628	3.9396	1.6884	0.5628
	Pre-phase 3	181.59	72.636	27.2385	18.159	12.7113	5.4477	1.8159
Europe								
Low cost	Pre-phase 1	25.72	10.288	3.858	2.572	1.8004	0.7716	0.2572
	Pre-phase 2	74.5	29.8	11.175	7.45	5.215	2.235	0.745
	Pre-phase 3	196.95	78.78	29.5425	19.695	13.7865	5.9085	1.9695
b. Biological entity-based intervention								
Heart								
High cost	Pre-phase 1	0	0	0	0	0	0	0
	Pre-phase 2	121	48.4	18.15	12.1	8.47	3.63	1.21
	Pre-phase 3	366.48	146.592	54.972	36.648	25.6536	10.9944	3.6648
USA								
Low cost	Pre-phase 1	40.41	16.164	6.0615	4.041	2.8287	1.2123	0.4041
	Pre-phase 2	157.43	62.972	23.6145	15.743	11.0201	4.7229	1.5743
	Pre-phase 3	397.2	158.88	59.58	39.72	27.804	11.916	3.972
High cost	Pre-phase 1	0	0	0	0	0	0	0
	Pre-phase 2	90.75	36.3	13.6125	9.075	6.3525	2.7225	0.9075
	Pre-phase 3	274.86	109.944	41.229	27.486	19.2402	8.2458	2.7486

Table 6 SOM rNPVs for each market using real-world data potential market share (numbers in millions of USD) *(Continued)*

Market penetration		100%	40%	15%	10%	7%	3%	1%
Europe								
Low cost	Pre-phase 1	30.31	12.124	4.5465	3.031	2.1217	0.9093	0.3031
	Pre-phase 2	118.07	47.228	17.7105	11.807	8.2649	3.5421	1.1807
	Pre-phase 3	297.9	119.16	44.685	29.79	20.853	8.937	2.979
abetes								
High cost	Pre-phase 1	41.21	16.484	6.1815	4.121	2.8847	1.2363	0.4121
	Pre-phase 2	205.99	82.396	30.8985	20.599	14.4193	6.1797	2.0599
	Pre-phase 3	592.19	236.876	88.8285	59.219	41.4533	17.7657	5.9219
USA								
Low cost	Pre-phase 1	90.96	36.384	13.644	9.096	6.3672	2.7288	0.9096
	Pre-phase 2	242.41	96.964	36.3615	24.241	16.9687	7.2723	2.4241
	Pre-phase 3	622.91	249.164	93.4365	62.291	43.6037	18.6873	6.2291
High cost	Pre-phase 1	20.61	8.244	3.0915	2.061	1.4427	0.6183	0.2061
	Pre-phase 2	102.99	41.196	15.4485	10.299	7.2093	3.0897	1.0299
	Pre-phase 3	296.09	118.436	44.4135	29.609	20.7263	8.8827	2.9609
Europe								
Low cost	Pre-phase 1	45.48	18.192	6.822	4.548	3.1836	1.3644	0.4548
	Pre-phase 2	121.21	48.484	18.1815	12.121	8.4847	3.6363	1.2121
	Pre-phase 3	311.45	124.58	46.7175	31.145	21.8015	9.3435	3.1145

a. rNPV calculations for different hypothetical SOM penetrations within the U.S.A and European markets for chemical entity based interventions for heart and diabetic disorders. The terminal market value used in the rNPV calculation was obtained by multiplying the SAM for the specific geography by the market penetrance percentage.
b. rNPV calculations for different hypothetical SOM penetrations within the USA and European markets for biological-based interventions for heart and diabetic disorders. The terminal market value used in the rNPV calculation was obtained by multiplying the SAM for the specific geography by the market penetrance percentage.

that the risk rate being used in the rNPV calculation is incorrect or illogical. We therefore decided to model a formula for a risk-rate that would be based on financial risk and a successful movement to market dynamics.

The first component of the formula is the financial risk. If an investor or business developer is assessing whether to invest in a R&D project, there is a financial risk related to the balance between what could happen to the money, the WACC and what is actually happening to the investment, the ROI. The argument is that to make the investment minimally worthwhile the ROI has to equal the WACC so the financial risk becomes 0. The overall objective is of course to make a profit that can be reinvested, but the first aim must be not to lose the money.

Using the formula = 100 − ((1/(WACC/ROI)) × 100) the baseline risk rate was determined; this would correspond to the risk that any investment made is going to fail. The value obtained based on the current WACC and ROI figures is 60.64%; this value corresponding to the time point 0 expenditure and the real possibility that the portfolio project may make no return. The risk rate would then need to be adjusted as a dynamic function of failure rate probability associated with movement from that time point to market release.

We used the phase-specific cumulative success rates indicated in Table 5, to generate the failure or progress risk rate (basically = 1—the success rate) and multiplied the

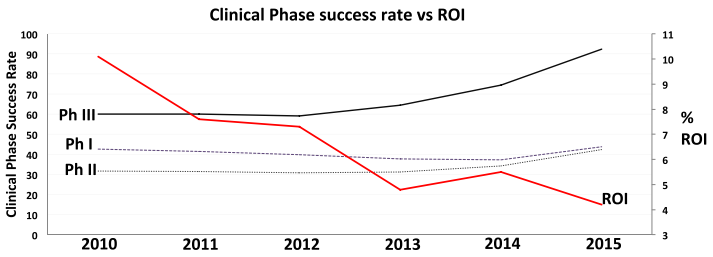


Fig. 2 Clinical trial rates for CVD vs generic ROI: Phase III clinical trial success rates have increased, but this has not been reflected in the ROI**. Da**ta for CVD success rates from 2010 to 2015 were obtained from Wong et al. (2018) and plotted against industry wide ROI on R&D figures obtained from Deloitte

baseline risk rate by this value to generate the phase-specific risk rate. For example, there is a 93.13% chance that for CVD an intervention entering phase 1 will not reach the market, therefore 93.13% of 60.64% would give the corresponding risk value to be used in the rNPV calculation at that phase.

The outcome phase-specific risk rates are indicated in Table 7, and only apply to the cardiovascular and endocrinological indications: the clinical phase rates for other indications from Wong and Siah's work would need to be performed for other indications. We have chosen to call these progress dependent dynamic risk rates (pd-DRR).

As indicated in Table 8, when a progress dependent dynamic risk rate (pd-DRR) is used in combination with market penetration SOM values, significantly lower valuations are obtained compared to using the IRR, but earlier stage innovations still retain value. This may be disappointing news for investors in life science, but it corresponds more to the market reality, and the harsh decision is that investments should only be made in potential best-in-class innovations (or ultra-orphan and orphan drug innovations if costs can be kept down).

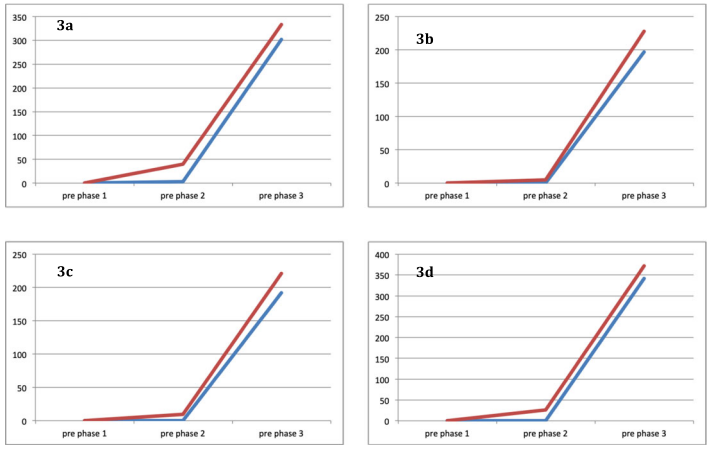


Fig. 3 rNPV calculations for the four interventions using indication specific FEC high and low costs and phase specific cumulative progressive success rate. **P**rogressive success rates indicated in Table 5 were used in the rNPV calculations for indication specific low (red line) and indication specific high (blue line) value calculations. **a** Chemical entity—heart. **b** Biological—heart. **c** Chemical entity—diabetes. **d** Biological—diabetes

Testing the model

To compare and test the models, we looked at three interventions that had been launched onto the market, ramipril (chemical entity—cardio), Reopro (biological—cardio), and dapagliflozin (chemical entity—non-insulin), obtaining total global sales volumes for each one as the terminal market value.

The first was ramipril (ramipril, n.d.). It is the generic version of an angiotensin-converting enzyme inhibitor (ACEi) first developed by Sanofi and marketed as Tritace. The first-in-class version of an ACEi was enalapril (Enalapril (2019)), and Tritace was developed as a best-in-class version. To enable Tritace to enter the TAM or global market, a pivotal trial was performed: it was a randomised, double-blind, controlled trial performed over a mean period of 5 years on 9541 patients at 276 sites in 19 countries, the results of which can be found online (HOPE trial (2000)). It was a landmark trial and resulted in the approval of the drug in 40 countries. The average cost per patient in a phase III clinical trial is around $42,000, which would mean that the pivotal phase III clinical study cost $2.0bn. An extension trial was performed for an additional 2.6 years corresponding to a phase IV study. Phase IV studies cost on average $16,500/patient (Biopharmaceutical Industry-Sponsored Clinical Trials, 2015; Long, 2017; Mcquire, 2011), implying an additional $410mn in costs. Analysis of published Sanofi annual reports (Sanofi annual reports and Form 20-Fs 2019) indicated that on average, Tritace generated $1bn/year in sales, which for the estimated 7 years of protection totalled $7bn, so technically a blockbuster drug. In sales, it has been reported that 30% of the value is related to manufacturing and 30% to general expenses (marketing and sales).

Therefore to generate the $7bn in sales, $2.1bn was spent on manufacturing, $2.1bn was spent on general expenses, $2.0bn on phase III, $0.41bn on phase IV, and $0.31bn on the R&D from discovery to the end of phase II. Meaning based on our numbers the drug created a total profit of $80mn ($0.08bn).

We performed similar calculations for the biological therapeutic Reopro (Eli Lilly SEC filings, Reopro Access data n.d.), which is used in the anticoagulant market, and the BMS/Astra Zeneca drug, dapagliflozin, a soldium-glucose co-transporter 2 inhibitor, for the treatment of type 2 diabetes (CDER, 2013; EMA report, 2012).

Unlike ramipril and Reopro which have been on the market for some time, dapagliflozin was only launched in 2014, it is a first-in-class drug, which is similar to many interventions designed for resolving diabetic patient needs, also needs to be tested for potential cardiovascular side effects (CDER, 2008). From 2015 to the first half of 2018 it has generated $3bn in sales (AstraZeneca 2019, AstraZeneca H1 2018 results (2018).

Table 7 Dynamic risk rates: rates that could be applied to the relevant stage being valued as a function of WACC and ROI (risk rates are indicated from their status in development to reimbursement)

New risk rate CVD by phase		
Status	CVD-specific phase rate	Endo/Meta-specific phase rate
Pre ph III	39.59	33.4
Pre ph I	51.59	49.99
Pre ph I	56.47	54.5
Discovery	58.06	56.84

Table 8 SOM rNPVs for each market using real-world data potential market share (numbers in millions of USD) using progress dependent dynamic risk rates (pd-DRR) for valuations

Market penetration		100%	40%	15%	10%	7%	3%	1%
a. Chemical entity-based intervention								
Heart								
High cost	Pre-phase 1	2.77	1.108	0.4155	0.277	0.1939	0.0831	0.0277
	Pre-phase 2	22.39	8.956	3.3585	2.239	1.5673	0.6717	0.2239
	Pre-phase 3	65.94	26.376	9.891	6.594	4.6158	1.9782	0.6594
USA								
Low cost	Pre-phase 1	9.22	3.688	1.383	0.922	0.6454	0.2766	0.0922
	Pre-phase 2	27.28	10.912	4.092	2.728	1.9096	0.8184	0.2728
	Pre-phase 3	70.43	28.172	10.5645	7.043	4.9301	2.1129	0.7043
High cost	Pre-phase 1	1.39	0.556	0.2085	0.139	0.0973	0.0417	0.0139
	Pre-phase 2	11.2	4.48	1.68	1.12	0.784	0.336	0.112
	Pre-phase 3	32.97	13.188	4.9455	3.297	2.3079	0.9891	0.3297
Europe								
Low cost	Pre-phase 1	4.61	1.844	0.6915	0.461	0.3227	0.1383	0.0461
	Pre-phase 2	13.64	5.456	2.046	1.364	0.9548	0.4092	0.1364
	Pre-phase 3	35.21	14.084	5.2815	3.521	2.4647	1.0563	0.3521
Diabetes								
High cost	Pre-phase 1	Negative	Negative	Negative	Negative	Negative	Negative	Negative
	Pre-phase 2	10.7	4.28	1.605	1.07	0.749	0.321	0.107
	Pre-phase 3	42.01	16.804	6.3015	4.201	2.9407	1.2603	0.4201
USA								
Low cost	Pre-phase 1	5.09	2.036	0.7635	0.509	0.3563	0.1527	0.0509
	Pre-phase 2	15.35	6.14	2.3025	1.535	1.0745	0.4605	0.1535
	Pre-phase 3	46.27	18.508	6.9405	4.627	3.2389	1.3881	0.4627
High cost	Pre-phase 1	Negative	Negative	Negative	Negative	Negative	Negative	Negative
	Pre-phase 2	5.63	2.252	0.8445	0.563	0.3941	0.1689	0.0563
	Pre-phase 3	22.11	8.844	3.3165	2.211	1.5477	0.6633	0.2211
Europe								
Low cost	Pre-phase 1	2.68	1.072	0.402	0.268	0.1876	0.0804	0.0268
	Pre-phase 2	8.08	3.232	1.212	0.808	0.5656	0.2424	0.0808
	Pre-phase 3	24.35	9.74	3.6525	2.435	1.7045	0.7305	0.2435
b. Biological entity-based intervention								
Heart								
High cost	Pre-phase 1	Negative	Negative	Negative	Negative	Negative	Negative	Negative
	Pre-phase 2	12.46	4.984	1.869	1.246	0.8722	0.3738	0.1246
	Pre-phase 3	45.57	18.228	6.8355	4.557	3.1899	1.3671	0.4557
USA								
Low cost	Pre-phase 1	3.63	1.452	0.5445	0.363	0.2541	0.1089	0.0363
	Pre-phase 2	17.35	6.94	2.6025	1.735	1.2145	0.5205	0.1735
	Pre-phase 3	50.05	20.02	7.5075	5.005	3.5035	1.5015	0.5005
High cost	Pre-phase 1	Negative	Negative	Negative	Negative	Negative	Negative	Negative
	Pre-phase 2	9.35	3.74	1.4025	0.935	0.6545	0.2805	0.0935
	Pre-phase 3	34.17	13.668	5.1255	3.417	2.3919	1.0251	0.3417

Table 8 SOM rNPVs for each market using real-world data potential market share (numbers in millions of USD) using progress dependent dynamic risk rates (pd-DRR) for valuations *(Continued)*

Market penetration		100%	40%	15%	10%	7%	3%	1%
Europe								
Low cost	Pre-phase 1	2.72	1.088	0.408	0.272	0.1904	0.0816	0.0272
	Pre-phase 2	13.02	5.208	1.953	1.302	0.9114	0.3906	0.1302
	Pre-phase 3	37.54	15.016	5.631	3.754	2.6278	1.1262	0.3754
Diabetes								
High cost	Pre-phase 1	3.03	1.212	0.4545	0.303	0.2121	0.0909	0.0303
	Pre-phase 2	21.65	8.66	3.2475	2.165	1.5155	0.6495	0.2165
	Pre-phase 3	72.66	29.064	10.899	7.266	5.0862	2.1798	0.7266
USA								
Low cost	Pre-phase 1	9.78	3.912	1.467	0.978	0.6846	0.2934	0.0978
	Pre-phase 2	26.54	10.616	3.981	2.654	1.8578	0.7962	0.2654
	Pre-phase 3	77.15	30.86	11.5725	7.715	5.4005	2.3145	0.7715
High cost	Pre-phase 1	1.51	0.604	0.2265	0.151	0.1057	0.0453	0.0151
	Pre-phase 2	10.82	4.328	1.623	1.082	0.7574	0.3246	0.1082
	Pre-phase 3	36.33	14.532	5.4495	3.633	2.5431	1.0899	0.3633
Europe								
Low cost	Pre-phase 1	4.89	1.956	0.7335	0.489	0.3423	0.1467	0.0489
	Pre-phase 2	13.27	5.308	1.9905	1.327	0.9289	0.3981	0.1327
	Pre-phase 3	38.57	15.428	5.7855	3.857	2.6999	1.1571	0.3857

a. rNPV calculations for different hypothetical SOM penetrations within the U.S.A and European markets for chemical entity based interventions for heart and diabetic disorders. The terminal market value used in the rNPV calculation was obtained by multiplying the SAM for the specific geography by the market penetrance percentage
b. rNPV calculations for different hypothetical SOM penetrations within the U.S.A and European markets for Biological based interventions for heart and diabetic disorders. The terminal market value used in the rNPV calculation was obtained by multiplying the SAM for the specific geography by the market penetrance percentage

Of this, the cost of goods and general expenses related to sales means that only $1.2bn potential margin exists. Unlike many other diseases, clinical trials for the creation of solutions for treating diabetes, the clinical trials are much shorter, typically less than a year. Nonetheless, to obtain approval, 11 phase III clinical trials were needed involving just under 5700 patients (CDER, 2013), following which authorities requested dedicated cardiovascular outcome trials (basically more phase III trials) which are still being performed on over 17,000 patients (Multicenter Trial to Evaluate the Effect of Dapagliflozin on the Incidence of Cardiovascular Events, 2012) as well as the 400 000 patient CVD-Real study (Wong & Blaha, 2017, AstraZeneca CVD-Real study, 2017). Given the shorter time frames for these trials, the costs have been estimated to be just under $1bn, but there are still 212 other clinical studies ongoing linked to this intervention (Trial database information (2019)). In a best-case scenario, 5 years after launch, integrating in the earlier clinical phases (37 phase I clinical trials were performed for this drug (CDER, 2013)) and R&D costs, this intervention is arguably still making a loss, with around 4 years of proprietary revenue-generating potential still on the books, however Janssen and Boehringer Ingelheim and Eli Lilly & Co. have launched next-generation versions of this type of intervention, which will erode revenue generation (Neville and Financial Times, 2017). Fundamentally, obtaining an ROI of 1 will be an achievement. To compensate for this, the drug is now presently being tested for treating type I diabetes.

We then used these development and sales figures to model the rNPV of the three different products at different phases using indication-specific success rates, looking specifically at the USA, the largest market, and assessing 40% market penetrance, arguably the highest possible market share when there are several competing products.

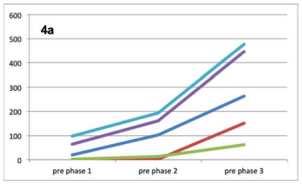
Illustrated in Fig. 4, which also includes the specific rNPVs, we compared indication-specific success rates in combination with IRR as a risk rate, cumulative clinical success rates in combination with IRR as a risk rate and the progress dependent risk rate, as well as the traditional generic success rates+IRR and low costs and the traditional Generic success rates+IRR and high costs. We also indicate the total sales volume, COGS/SGA and the profit, from which the development costs would have to be subtracted to obtain the final profit, only if the whole intervention was identified and developed in-house.

The problem starts if the intervention is being in-licenced from a start-up company that is using non-pertinent data to perform their pipeline rNPV calculations. Taking ramipril/Tritace as an example, if we hypothesise that a large company is looking to in-licence the intervention pre-phase III, their own historical evidence would indicate that obtain global sales of $7bn, after in-licencing they would need to spend a further $2.4bn on phase III/IV clinical studies. If the rNPV licence value for 40% access in the US market is calculated at $477.4mn, this would result in the larger company making a loss.

To further compound the problem, as the sales value corresponds to global sales, and rNPVs are additive, the total rNPV for global market access, at 40% market penetration using traditional Generic success rates+IRR and low costs would be $885 million, $827.48 million for traditional Generic success rates+IRR and High costs and $489.33 million for indication-specific success rates+IRR. In all three cases, the company licencing the innovation would make a loss. Only by using progressive market risk + IRR ($281.5 million total rNPV) or pd-DRR ($114.35 million total rNPV) calculations would the larger company make any profit. These outcomes may go some way to explaining why ROI's on R&D are so low, because portfolios are being prioritised based on innovations whose values are significantly overestimated.

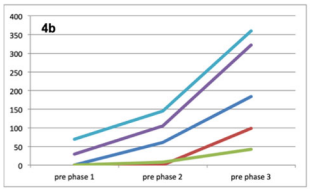
Strategies should potentially be redesigned generating more realistic stage-specific valuations that are lower thereby sharing the risk between the two entities; while future value could be realised for the small company based on a more generous revenue stream agreement, as the profit would increase, with potential extension into a revenue agreement on future generic versions or repositioning.

As a final small company modelling, we also wanted to assess the impact of geopolitical influence and political risk. Around the world in several regions and countries in which for generations significant capital has been invested into innovation development and the creation of a high technological critical mass, political changes have resulted these regions and countries putting in motion actions that would result in their removal from easy access to large trading geographies (Emmott, 2017; Saltman, 2013; Strauss, 2018). This would mean that for their innovations to be sold in the respective high value geography they would need to re-validate their innovations in the markets they would like to enter. Using the UK as a model and the data from Table 2, in which, based on NHS prices (Retained margin (category M)(2018)), the TAM value of antihypertensives in the UK is close to £60mn, we performed a variety of simulations to address the rNPVs at various stages, comparing IRR with the pd-DRR.



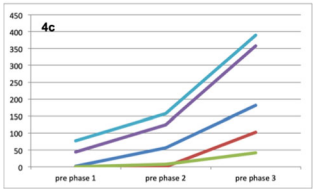
Ramipril	ind spec + IRR	prog +iRR	ind spec + pd DRR	Gen +IRR	Gen +IRR abbrev
pre phase 1	19.61	0	1.56	64.09	97.21
pre phase 2	102.31	1.67	13.75	160.39	193.35
pre phase 3	263.68	151.65	61.64	445.97	477.44

Sales	COGS/SGA	Pre dev Profit	Cost to dev.	Profit
$7bn	$4.2bn	$2.8bn	$2.72bn	$0.08bn



Reopro	ind spec + IRR	prog +iRR	ind spec + pd DRR	Gen +IRR	Gen +IRR abbrev
pre phase 1	0	0	0	29.03	69.28
pre phase 2	60.55	0	7.67	104.55	144.63
pre phase 3	183.71	98.84	42.65	321.81	360.32

Sales	COGS/SGA	Pre dev Profit	Cost to dev.	Profit
$5.44bn	$3.26bn	$2.17bn	$2bn	$0.017bn



Dapagliflozin	ind spec + IRR	prog +iRR	ind spec + pd DRR	Gen +IRR	Gen +IRR abbrev
pre phase 1	1.88	0	0	43.95	77.08
pre phase 2	56.31	0	6.94	123.82	156.78
pre phase 3	181.85	102.96	41.53	357.88	389.36

Sales	COGS/SGA	Pre dev Profit	Cost to dev.	Profit
$3bn	$1.8bn	$1.2bn	$1.1bn	$0.1bn

Fig. 4 Comparison of rNPV models used in study when applied to real world revenue generating medical interventions. **F**or three large revenue-generating medical interventions, rNPV modelling was performed using the 5 major simulation models of this study. Ramipril/Tritace (**a**), Reopro (**b**), and dapagliflozin(**c**) were used as examples, with real numbers indicated in the tables corresponding to rNPV values, as well as sales, COGS, pre-development profit, estimated cost to develop, and profit margin

The only stage and simulation at which a positive valuation could be reproducibly and realistically obtained, indicated in Table 9, was at post phase III with possible licence values ranging from £3mn to £6mn in value for the IRR model and less than £1mn for the pd-DRR model, despite possibly engaging anything from £50mn to £2bn in R&D costs.

Discussion

It has been argued that "the only thing you can guarantee about any valuation is that it is wrong" (Dillon, 2015), which prompted us to leverage our experiences in working from the early stages of R&D to mid-stage clinical validation, and from mid-stage clinical validation to marketing authorisation, reimbursement, market access and sales planning to identify potential reasons for holistic solutions to address the issue. No recent studies have been based on actual indication-specific clinical success rates and based on our observations and the accessibility of 15 years of up to date information (Thomas et al., n.d.; Wong et al., 2018), this has an enormous impact on value calculations.

It was also important to perform complementary simulations using well known and peer-reviewed sources of costs of development and historical success rates matched with the figures from the latest research to breakdown the components and figures that go into valuations to see where possible optimisations could be performed. The aim being to make valuations somewhat closer to reality mainly because based on our own professional experiences, the small companies' perspective of the market value of their own innovation pipeline is internally overvalued.

Table 9 The small company perspective and the impact of geopolitical changes and the risk of not being able to access large trading blocks, on values. (values indicated in $mn, using the latest success rates)

	100% market penetrance	40% market penetrance
IRR		
rNPV post Ph I	negative	negative
rNPV post Ph II	negative	negative
rNPV post Ph III	4.14	3.25
pd-DRR		
rNPV post Ph I	negative	negative
rNPV post Ph II	negative	negative
rNPV post Ph III	0.96	0.73

The outcomes of the simulations clearly indicated three key findings: the first, that every stakeholder in the development of novel interventions need to be fully integrated, and communicating costs with each other so that each one understands the full cost of development and how this impacts the stage-specific valuation; the second is the importance of indication-specific success rates, which in simulations reduced values by up to $500 million, and using real-world data $200 million; the third that from a small company perspective working typically within one regulatory and HTA specific geography, their own innovations should have their valuations performed using terminal market values defined by not only a regulatory licencing but also a value for money (as determined by HTA organisations and payers) assessment of their innovation vs. the standard of care in the given jurisdiction to determine ranges of possible market penetration. As already stated above, payer and HTA requirements, methods, and processes may vary across jurisdictions. However, certain characteristics overlap across hose jurisdictions, i.e. robustness of evidence/data, its meaningfulness and relevance to decision-makers. We took these into account for our work based on published evidence and our own experience conducting and advising on HTAs and payer discussions for recent healthcare technologies. We have further taken into account developments of payer and HA-specific early scientific advice services offered by payers and HTA organisations, both official and unofficial procedures (e.g. NICE scientific advice, EMA-HTA scientific advice, advisory boards, etc.) to further substantiate our work.

The rNPV outcomes obtained by using the full economic costs of the development that would be incurred by either one stakeholder performing everything in-house, or through multiple stakeholders transferring the technology upstream to a more relevant stakeholder versus abbreviated costs were dramatic, and if based on using accepted 'generic' values goes some way to explaining why the ROI on drug development is so low. Drugs reach the market where competing products drastically diminish the value of the innovation's applicability. This was further impacted by geographic separation into SAMs and further still when the simulation included real-world market penetration of interventions, in which there are multiple reimbursable interventions available. This would mean that all portfolio's would need to be re-evaluated to assess true value, and then tied into the companies logistical capacities, implementation approaches and strategies, and partnering possibilities to try to maximise value.

The use of a harmonised risk value inside the calculation would go a long way to informing all stakeholders, and while the IRR is standard, because its estimation is company specific, this can change significantly. We have proposed one alternative; it is clearly more realistic than existing risk rates when put into the context of real-world data but further modelling using as many different real-world examples, including from licencing deals, would inform the utility of its application.

For the small company CEO, business developer, or innovation specialist, it is clear that to generate a viable innovation that retains value during development, it needs to be a market leader, otherwise, business development and licencing decisions will arguably bias against further R&D. There are alternatives, that of repurposing or repositioning within the same indication has been proven to add significant value to interventions, such as the anti-TNFalpha antibodies, but this only occurs when the primary application has been achieved; whether such a factor can be integrated into early-stage development needs to be addressed. Similarly, irrespective of the valuation model, the significant increase in value from before phase II to after phase II studies, which represent the first pivotal evidence of clinical efficacy represents a critical node in intervention development, linking early-stage research with HTA based market release, and there are a number of lessons to be learned from phase II clinical studies that can be applied to early-stage research, which would likely impact the whole pipeline.

The resulting necessity to identify the true value of the innovation and the influencing factors indicates several approaches that should be taken during the whole development cycle. The obvious first one is to perform all studies from the bench to the bedside with the standard of care as a comparator; this includes all experimental and preclinical work, which would then facilitate the "kill early, kill frequently" strategy but without the decision being taken in isolation. An eye on the end goal and what is driving reimbursement clinical development programmes, especially phase 2 and 3 trials, need to include endpoints required by and relevant to HTA organisations and payers in a way that they are considered robust by them during their assessments and appraisals. Where this is not happening the company will face a high risk of negative reimbursement decision making and therefore none to (at best) very limited uptake and sales.

This implies that HTA specialists, who are familiar with approval and reimbursement policy should be involved throughout the clinical development programmes. These specialists can also provide advice and help with evidence generation alongside clinical trials to supplement clinical trial programmes to strengthen the data for use in HTAs and discussions with payers. Furthermore, these experts can also advise and help the company with the development of reimbursement dossiers and navigating reimbursement procedures.

There also needs to be a much closer link between the designs of the preclinical work and that during the clinical phases; performing preclinical animal work in the same way that human clinical work is now an accepted norm, but is just the starting point. Additional point to consider is the nature of the disease mapped against the components of the preclinical study; it is somewhat illogical to model an age-related degenerative disease in a transgenic model and perform intervention assessment two weeks after birth. This simply will not correspond to the primary or secondary clinical endpoints in a human. It would be better to front-load the risk and the cost by performing far more relevant and extensive preclinical work (including detailed analysis of off-target effects) rather than wait for the end of

a phase IIb and terminate the development. Similarly Wong et al. (2018) stated that the use of biomarkers in patient stratification was increasing success rates, which would also imply that the number of potential patients would be reduced, so a balancing act needs to be performed between the two approaches; one that can be resolved by internationalising as early as possible, with one key aim to ensure that preclinical and clinical outcomes are reproducible independent of geography. Additionally, the same biomarkers need to be included from the early stage and throughout the whole development.

There are limitations to the research performed here: the first is without doubt costing of development. While there was an impact on rNPV for the small company or business unit, they already know they are working within a high-risk endeavour and to a certain extent, given the long time frames, all possible opportunities from an innovation may not be apparent at the start of development. However, opportunistic costs of capital cannot be ignored; an investor wants to make a return and therefore prioritises investment based on this. The second is the real costs of development; these can balloon and decrease during early stages very easily, while the reported costs of clinical studies, we feel are an underestimate. In all costing models, only direct costs to the clinical centre are mentioned, the typical 100 to 120% indirect cost charged to a large company is not included, nor are the company related costs for the clinical trial such as their own staff and intervention manufacture, which can run into millions of dollars.

An additional limitation is related to clinical trial design: we are fortunate to have access to 15 years of modern clinical trial data success rates, but in many cases, progression, primary outcome achievement and eventual reimbursement definition is defined by the clinical trial design, whether it is randomised, non-randomised, crossover, matched pair, and so forth. It would be interesting to know within the different levels of success for each stage for each indication, whether there was a bias towards a clinical trial design that favoured a successful outcome.

This raises several avenues for future research, which we are presently modelling, including assessing successful marketed interventions for their major clinical study characteristics; assessing success rates in repositioning of approved interventions, what strategies were employed to achieve this, and how, related to product revenue maximisation using different valuation models for the different strategies, as well as mapping HTA requirements with early-stage plans. Finally, while modelled for life science products, the application of a more specific risk valuation system for other regulated industries such as aerospace, automotive, public infrastructure, civil engineering, and energy products warrants further investigation.

Conclusions

Generating value-producing medical interventions still poses significant challenges, with the maximum value being generated when significant and simultaneous markets are accessible. The implication is that internationalising via alliances or development partnerships with aligned companies in different trading geographies should be performed as early as possible and will increase values, especially for small companies. It is tempting to establish a subsidiary; however, to reduce unnecessary capital outlay, early-stage diverse geography-based duplication and reproduction of a strategic pipeline complementary innovation will increase the number of different SAM/SOMs that can be penetrated, simultaneously increasing the valuation of the innovation.

Each indication should be modelled individually, using the latest figures from the top ten reimbursed interventions in that pertinent geography as the comparator and then better define your innovation differentiators, understand its competitive advantage and the market holes. Many other options also exist that can be implemented from early stage to market release which simultaneously decrease risks and costs, many of which we routinely perform, but it is noteworthy that during our simulations single actions generate small gains, while comprehensive and cumulative changes significantly increase the value proposition of the innovations.

The early access to large markets is also critical; our simulations of high technological innovation in small market sizes make for worrying reading; if costs remain the same, but the terminal value is very small, the innovation generates no real value, which no investor will accept.

Finally, we believe we have identified a risk rate model that corresponds to the dynamics of medical intervention development, which relies less on hidden figures and is based upon a common understanding of investment decisions. While early-stage innovators and investors may not like the reduced valuation, the alternative is for them to invest and be told after a lot of money has been spent that there is no chance of a licence or gaining reimbursement and thus uptake and sales, while if a more realistic valuation is performed they may find a more amenable and also long term R&D partner in the purchaser.

This may be uncomfortable for many investors and small companies but the risk and future costs being carried by the entities responsible for actually converting the innovation into a commercial product is significantly greater than is presently being calculated.

Abbreviations

ACEi: Angiotensin-converting enzyme inhibitor; APAC: Asia-Pacific; CP: Critical path; COGS: Cost of goods; DCF: Discounted cash flow; Disc: Discovery phase in drug development; EMA: European Medical Agency; FDA: Food and Drug Administration; FEC: Full economic cost; HTA: Health Technology Assessment; IRR: Internal rate of return; NHS: National Health Service; OOP: Out of pocket; pd-DRR: Progress-dependent dynamic risk rate; Pre-clin: Pre-clinical phase in drug development; P&R: Pricing and reimbursement; R&D: Research and development; rNPV: Risk-adjusted net present value; ROI: Return on investment; SAM: Serviceable accessible market; SOM: Serviceable obtained market; TAM: Total accessible market; USA: United States of America; WACC: Weight-adjusted costs of capital

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Authors' contributions

JD performed all valuation calculations and analysis of early stage development related estimates, ML performed analysis of market share potentials and final reimbursement rates. All authors read and approved the final manuscript

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Availability of data and materials

rNPV modelling was performed using the accepted equation, extracted from (Svennebring & Wikberg, 2013): $rNPV = \sum_{n=1}^{N} \frac{C_n R_0}{(1+r)^{t(n)} R_n}$,

"where C_n is the n^{th} cash flow of N in total, R_0 and R_n is the estimated probability of obtaining the entire series of cash flows from the initiation of the project and from the n^{th} cash flow, respectively, r is the discount rate and $t(n)$ the time of the n^{th} cash flow"

Various automatic resources for rNPV calculation can be found online;
• https://www.nature.com/bioent/2003/030101/extref/nbt0901-813-S1.xls
• http://1zz10747jh9x3auhkivc05o5-wpengine.netdna-ssl.com/wp content/uploads/2011/03/Choose-Your-Own-Drug-Cost-Model.xls
Variables and data included in the rNPV calculations are indicated in this articles tables.
All data used to generate this publication are publicly available:
WACC: obtained from Stern NYC. http://people.stern.nyu.edu/adamodar/New_Home_Page/datafile/wacc.htm
Clinical success rates: obtained from supplementary material of Wong et al., 2018 at https://oup.silverchair-cdn.com/oup/backfile/Content_public/Journal/biostatistics/PAP/10.1093_biostatistics_kxx069/2/kxx069_supp.pdf?Expires=2147483647&Signature=E3kYWnqd0919IKiRRNcoJe~2rsNl1k7yNj82w3XfHaADd8UYqIvKonPEaKBzx72wklqXZc70lHJriqf6HNZP~hDO-Q8RlVXuPu1Z7ZiXBt0A58cL-ecYnWF8FDDYen1yxs3tY~PW0OrlLf-ymlLPufH0R34CErX51-x6tLsukrkNdOmcVdj0b0Xem~YwHSEjLbYT7qLGiTA5OpOVlMilHiSKUnANZf0E4c5wj7mFbgZm8PC0hMitCdI~aZWXCmytgIta2W3dfykTSa1cMTEt1VrJ0KcoXgvzvdUcbZ18yR66pgc6iGjEGFi5lUZ32kZR7-X2r01GJhtoP03~ZRFWyg__&Key-Pair-Id=APKAIE5G5CRDK6RD3PGA
ROI rates: obtained from Deloitte publication https://www2.deloitte.com/content/dam/Deloitte/uk/Documents/life-sciences-health-care/deloitte-uk-measuring-roi-pharma.pdf
DiMasi figures: obtained from http://www.fondazioneicinquecento.org/wp-content/uploads/woocommerce_uploads/2017/02/Tuft-study-J-Health-Economics.pdf
Booth figures: obtained from https://lifescivc.com/2014/11/a-billion-here-a-billion-there-the-cost-of-making-a-drug-revisited and https://lifescivc.com/2011/03/choose-your-own-numbers-crowdsourcing-the-cost-to-produce-a-new-drug/
Sertakaya figures: obtained from https://aspe.hhs.gov/report/examination-clinical-trial-costs-and-barriers-drug-development
NICE hypertensive drugs: obtained from https://www.statista.com/statistics/377952/top-ten-drugs-dispensed-for-hypertension-and-heart-failure-by-items-in-england/
Drug Sales AstraZeneca: obtained from https://www.astrazeneca.com/investor-relations/annual-reports.html
Drug sales Sanofi: obtained from https://www.sanofi.com/en/investors/reports-and-publications/financial-and-csr-reports/

Competing interests
The authors declare that they have no competing interests.

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