Recent data suggests that the probability of success in phase II clinical trials has the largest influence on R&D productivity of any of the factors explored across all phases of discovery and clinical development. However, failure rates in phase II (18.75%, 25%, and 32%) result in much lower than 0.01% success rates expected from the statistical power of these studies. Several methods have been proposed to reduce the risk of clinical trial failure. These methods include review of recorded assessments, novel clinical trial designs, Central Ratings in lieu of site ratings and innovative statistical methods, to name a few. However, to our knowledge, quantitative modeling has not been used to assess how much risk reduction methods may add to the R&D process.

The economic impact of applying risk reduction methods to CNS clinical trials is estimated using expected Net Present Value (eNPV). eNPV calculates all cash-flow expected, adjusted time and the probability of success. For example, a product that costs $20 to generate a 50% chance of generating $1 million in revenue might have an eNPV of $100 ($1 million / ($1/2) interest rate of 100%)

If there is any delay in the revenue, an annual discount rate must be applied to cover the cost of capital

- eNPV of a product that will deliver $1 billion peak annual sales is estimated under the conditions to the right:

- Year 1: $0
- Lifespan of Drug Post-Launch (in years): 18
- Probability of Success through Phase III: 97%
- Risk Reduced by 1%
- Risk Reduced by 20%
- Probability of Success through Phase IIb: 91%
- Probability of Success through Phase III: 97%
- Risk Adjusted NPV of Drug at Launch: $1,663,001,703
- Risk-Adjusted Value (eNPV) at Start of Phase III: $1,320,091,000
- Cumulative Probability of Launch at Start of Phase IIa: 43%
- Risk-adjusted cost of clinical trials: $78,710,375
- Probability of success at each phase and 

The Value of Risk Reduction in CNS Drug Development:

The Value of Risk Reduction in CNS Drug Development: Use of Expected Net Present Value (eNPV) as a Model

INTRODUCTION

The economic impact of applying risk reduction methods to CNS clinical trials is estimated using expected Net Present Value (eNPV). eNPV calculates all cash-flow expected, adjusted time and the probability of success at each phase of development, as well as future revenues.

At launch the NPV of a drug that will deliver $1 billion peak annual sales is estimated under the conditions to the right:

- Probability of Success: 97%
- Risk Reduced by 1%
- Risk Reduced by 20%
- Probability of Success through Phase III: 97%
- Year 1: $0
- Lifespan of Drug Post-Launch (in years): 18
- Probability of Success through Phase III: 97%
- Risk Adjusted NPV of Drug at Launch: $1,663,001,703
- Risk-Adjusted Value (eNPV) at Start of Phase III: $1,320,091,000
- Cumulative Probability of Launch at Start of Phase IIa: 43%
- Risk-adjusted cost of clinical trials: $78,710,375
- Probability of success at each phase and

Finally, eNPV at the start of Phase IIa is subtracted from the risk adjusted value of the drug, the time-discounted cost of bringing the drug from Phase IIa to launch using the phase durations and time-adjusted costs above.

\[ \text{eNPV} = \frac{(1 + \text{i})^{T} - \sum_{t=0}^{T} \text{CF}_t (1 + \text{i})^{-t}}{\text{i}} \]

where \( \text{i} \) is the discount rate, \( T \) is the time period of cash flow (i.e., year of sale), and \( \text{CF}_t \) is the cash flow for period \( t \).

The attractiveness and cost effectiveness of risk reduction methods is estimated by calculating the eNPV of the drug at launch, the eNPV at start of Phase IIa, and the Risk-Adjusted Value at Start of Phase III.

The Value of Risk Reduction in CNS Drug Development: Use of Expected Net Present Value (eNPV) as a Model

RESULTS

The eNPV of a $1 billion drug launch, using these assumptions, is estimated to be $1,663,000,000.

<table>
<thead>
<tr>
<th>Prob. of Success</th>
<th>Phase Duration</th>
<th>Cost</th>
</tr>
</thead>
<tbody>
<tr>
<td>80%</td>
<td>40</td>
<td>$6,000,000</td>
</tr>
<tr>
<td>91%</td>
<td>40</td>
<td>$15,000,000</td>
</tr>
<tr>
<td>98%</td>
<td>40</td>
<td>$30,000,000</td>
</tr>
<tr>
<td>99%</td>
<td>40</td>
<td>$60,000,000</td>
</tr>
<tr>
<td>99%</td>
<td>40</td>
<td>$90,000,000</td>
</tr>
</tbody>
</table>

The $1.663 billion value of the drug at the time of launch is diminished to $1.320 million adjusting for the cumulative probability of phase III clinical trial failure. As a result of risk reduction in each phase III study, the overall probability of launching the drug rises from 79% to 95%.

Increasing the probability of success in phase IIb by 2% increases the value of the drug at launch to $1.581 billion, thus increasing the eNPV by $252,663 million.

A 1% improvement in phase IIb probability of success increased eNPV by $75.9 million.

Based on the risk-adjusted value calculated above, the probability of success at each phase and 

Quantifying the dollar value reducing the risk of failure in phase I and II and understanding the significant return on investment afforded by methods that can reduce clinical trial failure rates even slightly, is critical to their potential to advance medical science by warranting false negatives that keep important new drugs from patients who need them. Serious consideration should be given, from both a financial and medical perspective, to methods for reducing attrition, especially in diseases with known high rates of failed trials, such as MODD, CNS, AD and many other CNS disorders.

There are many limitations to this analysis. All of the assumptions about sales, patent life, success rates of trials and phases, and development time periods are quite simplistic within the assumptions. - They may be very inappropriate for a specific drug development plan. However, all within the range of published literature, and the general approach taken here can be easily modified, for example, to fit a drug with 5 years of marketed patent life instead of 10. The quantitative estimates (1%) 20% potential impact of employing risk reduction methods are also illustrative assumptions that are easily modified without rigorous analysis. Further, these estimates do not include the incremental costs of employing risk reduction methods in clinical trials. Lastly, the simulations of phase II and III failure increments assume the development of a drug which is, in fact, safe and effective and ultimately approved for commercialization. However, additional simulations can be brought to bear across portfolios of successful and unsuccessful drugs, and there is also incremental value to improved signal detection in the case of unsuccessful drugs (i.e., faster).

Worth considering is that many aspects of improved signal detection are not assessed here, and in these cases we attempted to err conservatively on the conservative side. For example, more successful trials earlier could have several other positive impacts on eNPV, such as potential first-to-market advantages in regulatory review time, first-mover advantage in marketing and sales, etc.