M&S for the 100,000 foot view

Cutting the Gordian Knot: Using high value information for program design

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Following Marc’s dictum: Four slides or less

1. Simulation

2. Conclusions
Conclusions

Money Matters!
We can and should be doing strategy not just modeling and money matters.

1. Pharmacometricians (PMs) focus on interesting/complex modeling that leads to valuable treatments. But “We don’t do dollars, we do drugs.”
2. But DOLLARS are important, especially to executive management.
3. Drug-disease-trial-program models could provide a data-driven basis for modeling the finances of development and the probability of registration/launch.
4. Using dollars you can compare the value of alternative strategies
5. What counts is how well you make the decision, not how good the model fits.
Fini
Value of Information (VOI) or “What I learned about drug development by playing Poker on Friday nights…”

The two endeavours are not so different...

1. The goal is to make money
2. Both are betting games
3. You (usually*) have to pay a lot for information to keep playing
4. You have already spent what you put into the pot—the question is: “Is it profitable to ante-up to stay in the game?”

“You have to know when to hold ‘em, know when to fold ’em”

*Except when you can use literature data to understand your drug’s behavior
1.0 The way to value a trial is in dollars

VOI from the trial = Increase in Expected Future Value of the Drug - Cost of the Trial

1. Drug development trials are a corporate investment or purchase of information about a compound.
   a. Information becomes the fact basis for making future decision about drug development.
   b. Future decisions can be about this compound, other compounds (backups, in-license candidates, competitive drug, etc), marketing, development strategies, acquisitions and mergers, etc.

2. An inconclusive trial has no or negative value of information.
   a. The value of the information depends upon the future decisions and the value of the outcomes resulting from those decisions.
   b. Short term goals are simply surrogates for long-term goals.
   c. In order to directly compute the value of information the outcomes need to be measured in the same numeraire as the investment, i.e., dollars.
2.0 Net present Value

Bankers require interest for loaning you money. If you agree to pay $c back in year $y$, then a banker will loan you

$$\text{Present Value} = \frac{c}{(1+r)^y}$$

$r$ is the discount rate or time value of money. Given launch, drugs typically are expected to earn cash flow (cash each year) similar to the LHS of the figure below. These amounts are “net of any expenditures” in each year. The NPV is

$$\text{Net Present Value} = - \sum_{j=\text{now}}^{\text{launch}} \frac{c_j}{(1+r)^j} + \sum_{j=\text{launch}}^{T_{\pi}} \frac{c_j}{(1+r)^j}$$

where $T_{\pi}$ = year of patent expiry and $c_j$ are development costs or net cash flows after launch.

Delaying the launch date loses the cash flows at patent expiry. This reduces the NPV as shown in the figure on the RHS below.
3.0 Value of Information (cont.)

Case Study: The drug was a new MOA for schizophrenia. Hopes to be the new SOC.
- About 12 years on the patent, phase I completed. MTD 80 mg due to QTc.
- The expected peak cash flow if a new SOC is $1.7B or an expected NPV of $5.9B
- Planned a 48 patient POC in 3 centers against placebo (must beat Haldol to be market competitive.) Cost: $1M +1.25 years.
- Phase IIIB+III would cost $60M. The no POC Expected Value is: $236M.
3.0 Value of Information (cont.)

The POC trial is under powered.

Without the POC, the NPV was $5.9B given success. With the POC, the NPV is $5.2B due to the 1.25 year delay to do the trial.

The VOI is the value with the POC-the value without the POC, or

(With POC = $210 M) - (Without POC = $236 M) = a loss of $26M by performing the POC trial.
4.0 Using Portfolio Tools to Choose the Order of Development of Two Indications (Why its not a “no-brainer!”)

*Case Study: An oral pro-drug (IL-1) for the treatment of autoimmune disease such as psoriasis (PSO) and rheumatoid arthritis (RA).*

The team sat in every meeting discussing(!) whether to do RA first or PSO first.

The drug had low bioavailability (4 gm BID or TID) and was expensive ($25K/yr)

Chronic plaque PSO has ~ 1.4M potential patients reduced by 95% due to the cost. Optimistically the peak revenue would be about $1.55B/yr. Chance of becoming SOC near 0.

Chronic RA has about half the target patients, but poorer treatments.

Roughly the same # of patients could use the drug. Peak revenue would be about 1.6B/yr. Chance of becoming the SOC is small, but significant. This would give a boost to revenues by a factor of five or six.

The RA trial is more complex to run and takes somewhat longer.

The development costs were not very different $70-80M.
4.0 Using Portfolio Tools to Choose the Order of Development of Two Indications (cont.)

This is a small portfolio problem consisting of two correlated indications (the chance of success of the second is increased given the success of the first).

The strategies discussed are listed in the table and Influence diagrams for two are shown below.
4.0 Using Portfolio Tools to Choose the Order of Development of Two Indications (cont.)

At the base assumptions, RA then PSO has the highest value.

Sensitivities show that the order flip-flops; Conservative RA->PSO; Aggressive POS->RA

Essentially, we can flip a coin.

But, wait... Why not do both at the same time?

Value = $5,410

(42% greater)
Conclusions

1. **Money matters!**

2. **Dollars/Euros/Yen are an appropriate metric for valuing the trial and trial design.**

3. **Time is money. Monetize the cost of delay.**

4. **Money matters because it allows you to value the contribution of your modeling, and to focus your attention on valuable parts of the model.**

5. **For a $5B dollar drug every week saved by M&S is worth $14M.**

6. **Ask Big Questions! Play BIGGER!**
For this material and areas that can enhance your outlook considerably.
Bibliography


Bibliography (cont.)


2.0 A PKPD Treatment Decision Evaluation Example

- The decision is dose regimen. The deterministic relationships are embodied in the first order differential equation of a one-compartment model.
- There is uncertainty about the parameters of the PK-model.
- The Plasma concentration due to absorption is determined given the parameters.
- The drug effect is an Emax model with uncertain parameters.
- The clinical utility (value metric) is determined from the dose regimen and the drug effect.

NB: This is a decision-focused problem, NOT a parameter estimation problem. The influence diagram for the estimation problem is more appropriately a WinBUGS doodle.
- Dose Regimen
- Plasma Concentration due to Absorption
- Ka
- f/V
- dC/dt
- K
- C(t)
- Emax
- EC50
- Drug Effect
- Value
- α
3.0 Value of Information (VOI)

- Decisions are choices among alternative investments made to influence outcomes that are rewarding (positive & negative).

- Suppose you have the opportunity to buy information ($I$) before making the decision. $I$ is valuable if and only if:
  - You can change the choice so as to lead to better (bigger) outcomes (different choice)
  - You can create new alternatives that have more rewarding outcomes (different choice)
  - The posterior probability of the valuable outcomes of your current choice are increased (higher expected value for the same choice)

- Otherwise $I$ has no value

- Drug development is a sequence of investments purchasing information leading to better therapies (high market rewards)
3.1 Value Measures

Different stakeholders have different measures of value:

- Patients and their agents want the highest clinical utility of their treatment regimen.
- Patients can only pay a maximum amount to avoid the risk of death ($/micro-mort).
- The FDA wants the population average clinical utility to be as large as possible.
- The corporate shareholders or investors want the highest cash flow in return for their sequence of investments.