Berry Consultants
Statistical Innovation

FACTS

The Business Benefits of using QUOTES to estimate the NPV/ROI of a clinical development program

QUOTES enables quantitative, objective decisions about the size and design of the clinical trials in a clinical development program, and the decision criteria for proceeding from stage to stage. It helps this process by providing a standard, repeatable, framework for estimating the costs, duration, probability of success and revenue of a clinical development program – and hence the eNPV or ROI of the program under a set of assumptions.

In the estimation of the value or ROI of a clinical development program there are many uncertainties, in particular: “How large is the effect size of the treatment?”, “How quickly will subjects be recruited in the clinical trials?”, and “How valuable will the treatment be when and if it makes it to market?”.

QUOTES averages over the ranges of these uncertainties given the best assumptions and estimates available the time. This enables different design choices or strategies to be compared and ranked on a level playing field. Allowing the options with the highest expected value and the most robust performance to be identified. Perhaps this is QUOTES’s most important feature – giving statisticians a better way to talk to management.

As a side-effect of this process it provides a test of the assumptions and estimates that are used, by making clear the consequences of those assumptions and estimates.

QUOTES™

QUOTES is a novel and innovative software package that helps address the question: How does my company best spend its research dollars? It simulates a drug development program from Phase II trial to market in order to generate estimates of NPV or ROI. This in turn allows the clinical team, and those investing in the treatment, to explore the trade-offs of speed, cost and precision, and optimise the design choices along the development path.

QUOTES evaluates the Phase II & Phase III (or just Phase III) stages of drug development in order to estimate: the likely probability of technical success, time to market, and profit. And hence estimate expected Net Present Value (eNPV) and expected Return on Investment (ROI). This in turn allows different development program options to be compared in terms of their relative value and hence the optimal version of the program selected.

For example, and at its simplest, how large should the Phase III be? Slightly more complicated, how large should Phase II be, what level of confidence in efficacy should be required before proceeding to Phase III and how large should Phase III be? More complicated still – how many doses should be studied in Phase II, should Phase II use an adaptive trial design as well as how large should it be?

Uncertainties Everywhere

The value of a clinical development program depends on many factors, many of which are highly uncertain:

- What the clinical benefit and safety of the treatment will be.
- What the best way to administer the treatment (dose, regimen, combination with other treatments, etc.) will be.
- How long it will take to get to market.
- What the net revenue will be once in the market.
- How long a price premium can be maintained in the market.

QUOTES estimates the expected value of the program given all these uncertainties. Without a software package to range over the uncertainties, reliably and consistently, deriving such estimates is almost impossible. It is certainly time consuming and error prone.

Better Decisions

Faced with complex evaluations with multiple dimensions of uncertainty, without tools to help, the natural outcome is for our human cognitive biases to take over. For example:

- Risk aversion: “If I do an innovative trial and the treatment fails, I’ll get some blame, but if I just do the standard trial and the treatment fails no-one can blame me”.
- Optimism bias: decisions may reflect the desires and prejudices of the clinical team – which will be that their treatment will be successful but by analysing the impact of the Phase II design decisions on eNPV and ROI the value of features in the Phase II trial such as being able to stop early for futility
- Hindsight bias: the outcome of previous trials seem with hindsight to have been inevitable, the uncertainty before these trials were run is forgotten or diminished, this then encourages people to think that they can avoid the difficult planning to cope with the uncertainty in a future trial.
- Poor judgment under uncertainty[1]: the natural human response is to make some simplifying assumptions that shrink the uncertainty – that lead to biases in their judgement.

QUOTES provides a framework in to which estimates and assumptions are placed. This makes them transparent and quantified so they can be challenged and debated. QUOTES’s ability to swiftly re-calculate the eNPV and ROI means that sensitivity analyses can easily performed, allowing the team to focus on refining the most influential inputs.

Re-use of QUOTES across projects allows the different stakeholders to become accustomed to providing the required estimates and assumptions, encouraging thought about the full process of trial design.

Better Communication

To perform the estimation QUOTES requires inputs with regard to trial costs, accrual speeds, and expected revenues as well as simulations of the clinical trials. This allows the different key groups involved in the development program to come together to pool the inputs and review the results of the estimates. It will be commonplace that these meetings surface important information that one group has that others were unaware of.

Thus using QUOTES can help break down the barriers between the silos that inevitably arise in large organisations as groups optimize locally the processes that they perform.

Typical experience – there is no silver bullet

When this simulation approach has been used to refine an optimize a particular approach, we have always found the optimal values for different design choices – for instance the size of Phase II, the size of Phase III, the threshold used for the go-no decision at the end of Phase II – have had a range where the eNPV has been close to the maximum, and there is not one design choice that makes the difference. Rather we have found that it is the accumulation of increases in value by optimizing a number of parameters and design choices that eventually leads to a marked improvement in value compared to the starting position.

Conversely where this approach has been used to select between radically different approaches it has usually been the case that a clear cut winner has appeared early on.

For more information

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[1] “Judgement under Uncertainty” Amos Tversky, Daniel Kahneman, Science 27th Sept 1974