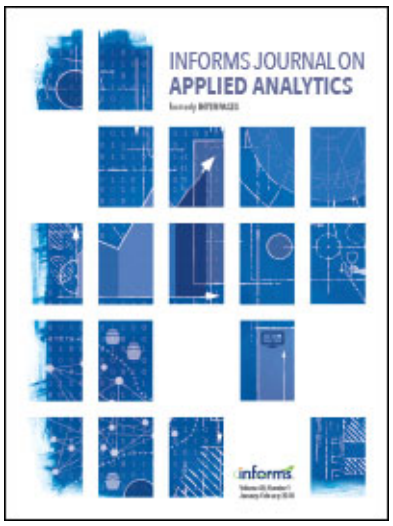

Interfaces

Publication details, including instructions for authors and subscription information:
http://pubsonline.informs.org

Practice Abstracts

Donald L. Keefer,

To cite this article:
Donald L. Keefer, (2004) Practice Abstracts. Interfaces 34(3):206-207. https://doi.org/10.1287/inte.1040.0079

Interfaces
Vol. 34, No. 3, May–June 2004, pp. 206–207
ISSN 0092-2102 | EISSN 1526-551X | 04 | 3403 | 0206

informs

DOI 10.1287/inte.1040.0079

Practice Abstracts

Donald L. Keefer
Department of Supply Chain Management, Arizona State University, PO Box 874706, Tempe, Arizona 85287-4706, don.keefer@asu.edu

"Practice Abstracts" carries short reports of specific current or recent OR/MS projects. Often these reports are based on existing documents, such as internal reports or company newsletters. We hope that these abstracts will be accessible, interesting, and valuable to practitioners in other organizations. Contributions should be sent for evaluation to the editor of "Practice Abstracts," Donald L. Keefer, Department of Supply Chain Management, Arizona State University, Box 874706, Tempe, Arizona 85287-4706 (don.keefer@asu.edu).

Key words: industries: pharmaceutical; decision analysis: applications.

Decision Analysis to Evaluate Proof-of-Principle Trial Design for a New Drug Candidate

Johnson & Johnson Pharmaceutical Research & Development (J&J PRD) used decision analysis tools, including Bayesian updating of probabilities, to aid in determining the best testing strategy to pursue for a new drug candidate, the identity of which remains confidential. We condensed a complex real-life problem into a manageable model that provided practical insights in a timely fashion.

The drug candidate had passed human safety trials (Phase 1), and was being considered for a full development program (Phases 2b and 3), with a projected investment of the order of $200 million over five years. Before committing to full development, management wanted to consider further testing via proof-of-principle (POP), or Phase 2a, clinical trials, which are designed to provide information to aid in major development decisions at relatively low cost (roughly $10–$20 million). In this instance, the clinical development issues included (1) whether or not to conduct a POP trial and, if so, what type of POP trial to conduct, and (2) whether or not to include an "active comparator arm" in the trial. The global medical leader for this drug, a key member of the interdisciplinary drug development team responsible for this compound who is in charge of clinical development strategies, asked us as members of the decision analysis department within J&J PRD to provide assistance in choosing a clinical development strategy.

Each of the four clinical trial alternatives under consideration included one placebo arm, one or more test arms, and an active comparator arm (an *arm* essentially is a group of patients). A placebo is an inactive substance that is given to patients in the control group, who form the baseline against which the group receiving the test drug is compared. Patients in the active comparator arm get an already approved drug that is known to be efficacious. Including this arm can be helpful in detecting a failed trial in which a strong placebo effect confounds detection of the test drug's true effect. If the active comparator fails along with the test drug, then the posterior probability of a false negative increases.

The four clinical trial alternatives for the POP trial were as follows: Design A involved four arms—one placebo arm, two trial arms with different dosing levels, and a possible active comparator arm. Design B was similar to Design A but with only one trial arm, that is, only one dosing level. Design C was essentially equivalent to replicating Design B (that is, performing two separate trials based on Design B). Design D was similar to Design B but with a bigger sample size for the trial arm.

Thus, the three basic decisions were (1) Is it optimal to do a POP trial? (2) Which POP trial design is the best? (3) Should there be an active comparator arm in the trial? The third issue was actually identified during the analysis process; the team had not originally considered it as a decision. We used decision trees to represent and analyze the various sequential strategies and to find the best strategy with respect to net present value (NPV).

To get the necessary probability data, we combined judgmental assessments, using standard decision analysis procedures, with Bayesian preposterior analysis. Working with an expert panel consisting of three clinicians, a biostatistician, and a project manager, we developed an influence diagram (Figure 1) to describe the relationships among efficacy, the placebo effect, and the trial results. We used this diagram to guide the probability assessment process and subsequent calculations. We first assessed the prior probability of the underlying efficacy of the drug

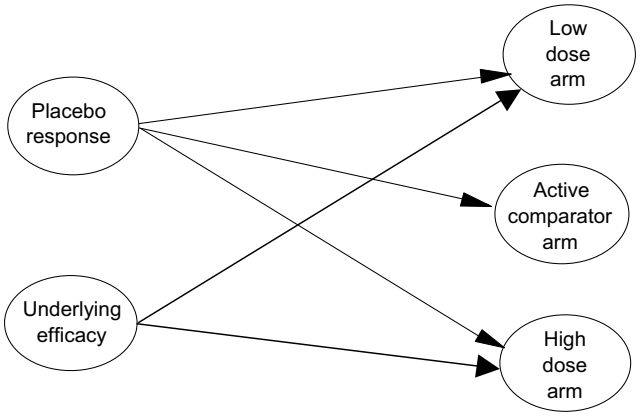

Figure 1: This influence diagram shows the five random variables of interest and their relationships. The nodes represent uncertainties, and an arc between two nodes indicates probabilistic dependence between them. The outcomes of the two trial arms using the test drug (low dose and high dose) are directly affected by the underlying true efficacy and the actual placebo response. The comparator arm outcome is influenced only by the placebo response.

candidate at four levels—not effective at any level, effective at lower dose, effective at higher dose, and effective at both doses—while treating efficacy (effectiveness) as a dichotomous variable at each dose. Next, we assessed the probabilities of different levels of placebo response—strong, typical, and weak. We then assessed the conditional probabilities of the different trial arms and the active comparator arm being positive (sensitivity and specificity) given levels of efficacy and the placebo response, for example,

$$Prob(\textit{high dose arm positive} \mid \textit{efficacy at low dose and typical placebo response}).$$

Based on the influence diagram, we calculated posterior probabilities for different efficacy levels conditional upon the observation of different trial results, initially using Excel and then switching to DPL decision analysis software (a product of Syncopation Software Ltd.). For example, we calculated

$$Prob(\textit{efficacy at low dose} \mid \textit{low dose arm pos., high dose arm neg., comparator pos.}).$$

Once we had calculated the necessary posterior probabilities, we conducted a decision analysis using DPL to determine which trial, if any, should be performed. In addition to the initial decisions regarding a POP trial and the related uncertainties in the POP results, the decision tree represented the subsequent full-development decision along with the uncertainty in the success of the development phase, conditional on test results where appropriate. On paths where development was successful, the NPVs included the full (mean) commercial value less the development costs.

Based on expected NPV, we showed it was optimal to conduct the POP trial and use Design A, which had an expected NPV $9 million greater than that of Design B, the next best alternative. We also showed that including a comparator arm does not add any information value for decision making in this specific situation. The project team benefited in several ways:

—The team got confirmation that doing the POP trial will help it make a better decision resulting in higher expected NPV.

—The team got an objective assessment to help it pick the best trial design, which it could implement immediately.

—The analysis also helped the team to rethink the need for an active comparator arm and ensure that it is included for the right reasons.

The team appreciated the analysis, especially the fact that it enabled it to use a model based on sound decision analysis principles as opposed to relying upon Individual opinions and biases. The analysis also helped create an understanding of the limited value of the comparator arm in this situation and introduced a constructive debate regarding its value. Management accepted our recommendations regarding the choice of the trial design, and similar analyses are underway in other contexts.

Vish Viswanathan and Rick Bayney
Johnson & Johnson Pharmaceutical Research & Development, L.L.C., 1125 Trenton-Harbourton Road, PO Box 200, Titusville, New Jersey 08560 {vviswana@prdus.jnj.com, rbayney@prdus.jnj.com}