

Interfix: Replication of Predictive Power Results in FDA Submission of Interfix™ Device.

Goal: To replicate the predictive power results presented to the FDA in the submission dossier of Interfix™.

Background: Interfix™ device is indicated in spinal procedures of patients with degenerative disk diseases. It was approved by the FDA in May 1999, based on a Bayesian interim analysis of phase III trial. A Bayesian predictive modeling of the future success rate was used that led to an early stop of the trial for efficacy. No prior information was used.

Bayesian Model: The success rate is a binary response that was analysed using an independent proportions model.

Uniform priors were selected for the control and Interfix devices:
 $p_0 \sim \text{beta}(1,1)$, and $p_1 \sim \text{beta}(1,1)$.

Adaptive design: At the time of interim analysis, the data were as follows:

Table 1. Interim Success Rates

Group	N	# success	Success rate
Interfix	67	37	55.2%
Control	45	17	37.8%

There were approximately 100 Interfix device patients who were not yet due for their end-of –study evaluation at that time. Final analysis was planned after these patients in the Interfix arm had completed a 24-month observation period.

Decision: The equivalence of Interfix was assessed based on non-inferiority testing procedure on the posterior distribution:

$$\Pr[p_1 > p_0 - \text{delta}] \geq 96\%,$$

where delta is a non-inferiority margin chosen based on clinical relevance (between 0 and 10% here). A value of 0 corresponds to Interfix being superior to control.

The predictive probability of success (PPS) at study end, when N=167 patients in the Interfix arm :

$$\Pr[p_1(N=167) > p_0 - \text{delta}]$$

was also estimated at the time of the interim analysis using simulations.

A decision to stop the study early for efficacy was made if the predictive power for non-inferiority was large (ie>95%).

Simulation: The predictive distribution of individual patient responses was estimated at the time of interim. A random sample from this individual predictive distribution was exported from Decimaker. Then, responses for the next 100 Interfix patients in the trial were randomly sampled from this predictive set using the resampling feature in Decimaker. Five thousands studies were simulated, in which the predictive probability of success was estimated. Power was then estimated as the frequency of studies in which PPS was larger than 96%.

Results: The interim posterior probability of non-inferiority and the predictive power results at study completion are summarized below for several values of delta:

Table 2. Interim probability and predictive power of non-inferiority.

Delta	Interim Probability of Equivalence	Predictive Power
0	0.96	0.834
0.01	0.97	0.880
0.02	0.98	0.984
0.03	0.98	0.991
0.04	0.98	0.998
0.05	0.99	0.999
0.06	0.99	0.999
0.07	0.99	1.000
0.08	0.99	1.000
0.09	0.99	1.000
0.10	0.99	1.000

At the interim analysis, there was a high probability ($\geq 96\%$) that Interfix is non-inferior, and even superior, to the standard of care. In the Interfix Summary of Safety and Effectiveness (SSE) document, a frequentist approach was used to compare success rates from Table 1 ($\Delta=0$, $p=0.0527$). The Bayesian analysis is thus more powerful than the frequentist approach in this case study.

The equivalence conclusion will very likely ($\geq 98\%$) remain true at study end, considering a non-inferiority margin of at least 2%. Based on these results, the remaining patients in the study will likely not impact the current non-inferiority conclusion. They also have 83.4% chances of not impacting the Bayesian superiority conclusion.

Below, we have reproduced the predictive probability plot from the SSE document. The actual method used to estimate these results was not described in the SSE document. Hence, it may likely differ from the proposed method in this report. Despite this possible discrepancy, results are very similar and conclusions about Interfix non-inferiority remain the same.

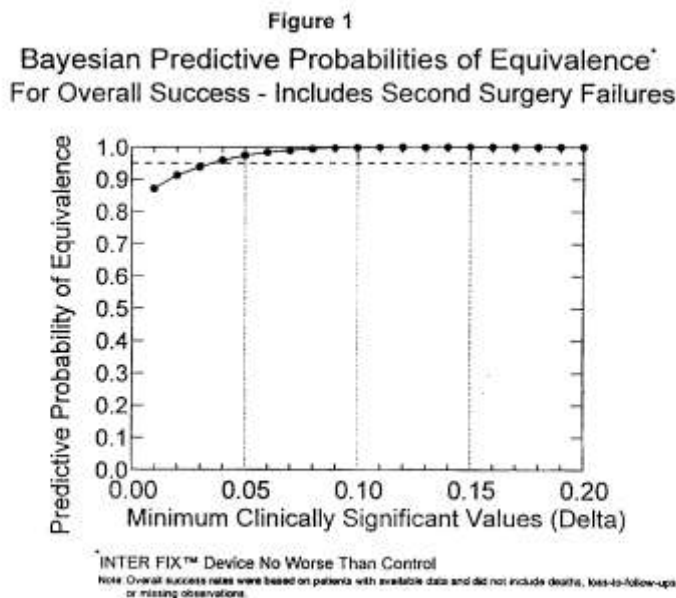


Figure 1. Predictive power plot taken from the Interfix SSE document.

Decimaker: The Decimaker study project may be found [here](#).

References:

- INTERFIX FDA Summary of Safety and Effectiveness Document: <http://www.fda.gov/cdrh/pdf/p970015b.pdf>.
- FDA CDRH. Guidance for the Use of Bayesian Statistics in Medical Device Clinical Trials - Draft Guidance for Industry and FDA Staff. <http://www.fda.gov/cdrh/osb/guidance/1601.html>, May 2006.