厦門大學

Operation and research program case report

Idiopathic Pulmonary Fibrosis

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2020.11.10

Catalogue

1.Case analysis

Through the interpretation and analysis of the case, we summarize the basic points made in the case.

Marnac has two drugs: steroids and non-steroids, both of which are effective in suppressing IPF. The funds available to Marnac are only able to continue to invest in one drug, so a decision has to be made for Marnac.

Initially, non-steroids had a 14.85% chance of passing FDA inspection, while steroids had an 11% chance of passing FDA inspection. Whereas choosing non-steroids costs $247.5 million, choosing steroids costs $125.1 million. The expected benefit of non-steroids is $1762.5 million, while the expected benefit of steroids is $1251 million.

And with some data in hand, Marnac has some more detailed information on non-steroids.

The non-steroid application requires three stages. The first phase is the IND phase, which costs $74.25 million and has a 40% probability of approval; the second phase is the clinical trial phase, which has three phases: phase 1, which costs $15.2 million and has a 75% probability of approval, and phase 2, which costs $23.4 million and has a 48% probability of approval. Phase 3 costs $86.5 million and has a 64% probability of passing; Phase 3, the NDA phase, costs $48.15 million and has a 90% probability of passing.

Stage	Stage 1	Stage 2			Stage 3	Total
		Phase 1	Phase 2	Phase 3		
Cost（in Million）	$74.25	$15.2	$23.4	$86.5	$48.15	247.5
Probability of pass	40%	75%	48%	64%	90%	8.29%

In fact, Marnac chose a non-steroidal drug and has already completed testing of phase 1 in the clinical trial phase.

Now, Marnac is considering selling the subsequent license to InterMune, and InterMune is considering whether to accept the sale of this license.

For InterMune, if they choose to accept the license, they will start with a clinical trial phase of phase 2. They will also have the corresponding information on the cost of the process, the chances of passing, and the final payoff, all of which will be shown in the table.

Stage	Up front payment	Stage 2			Stage 3
		Phase 2	Phase 2 do over	Phase 3	NDA
Cost（in Million）	18.8	52.5	52.5	195	195
Probability of pass	100%	33%	35%	20%	20%（of FDA）
					20%（of EMA）
					45%（of both）

And for phase 2 and every subsequent clinical trial, InterMune will have to pay an additional $14.5 million, regardless of whether the trial is successful or not.

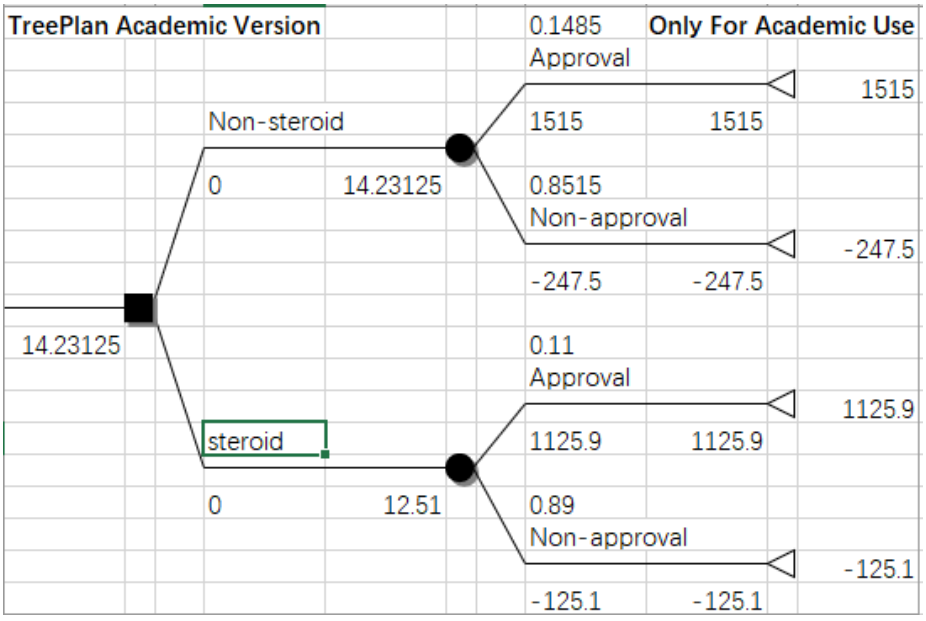
InterMune will make $825 million if it receives FDA approval, $1113.75 million if it receives EMA approval, and $1762.5 million if it receives both FDA and EMA approval. (These profits are before expenses)

2. Questions & Answers

2.1 Question 1

Assignment Questions pertaining to the initial decision of Marnac:

1. What is the structure of Margolin's decision to continue development of the nonsteroid pirfenidone vs. the steroid? In particular, how many decisions are there? Construct a graphical representation of this decision.



As you can see, we used the decision tree structure to analyze the problem.

As shown in the decision tree, there is one decision point.

2. Which alternative, the steroid or non-steroid pirfenidone, has the higher expected value?

As shown in the decision tree:

E(Steriod)= 12.51

E(non-steroid pirfenidone)= 14.2315

Therefore, non-steroid pirfenidone has the higher expected value.

3. Which alternative, the steroid or pirfenidone, has the higher risk?

As to the steroid, the probability of non-approval is 0.8515.

As to the pirfenidone, the probability of non-approval is 0.89.

4. How has risk been handled?

Using decision tree as a tool, we calculate the expected value of different decisions according to Bayesian decision criterion. By choosing decisions with high expected value, we do our best to

handle risk.

5. "Cash is king" often refers to cash flow as being the reason that a business ultimately closes. If Marnac can sustain at most an affordable loss of $200M without jeopardizing its continued existence, what decision should it make?

Assuming Marnac fails to obtain the approval after choosing Pirfenidone, the loss is $247.5M.

Assuming Marnac chooses Steroid without approval, the loss is $125.1M.

If Marnac can sustain at most an affordable loss of $200M, then Marnac should make a decision of steriod.

6. Based on the tree, why do you think Marnac (Margolin) decided to pursue pirfenidone rather than the steroid?

This decision tree has only one decision node. For this decision node, the expected revenue of each branch is compared, and then the scheme of the branch with the maximum expected revenue is selected.In fact, for any decision tree, the backward induction procedure will always generate the optimal strategy after the probability is calculated on the branch emitted from the Event Node.

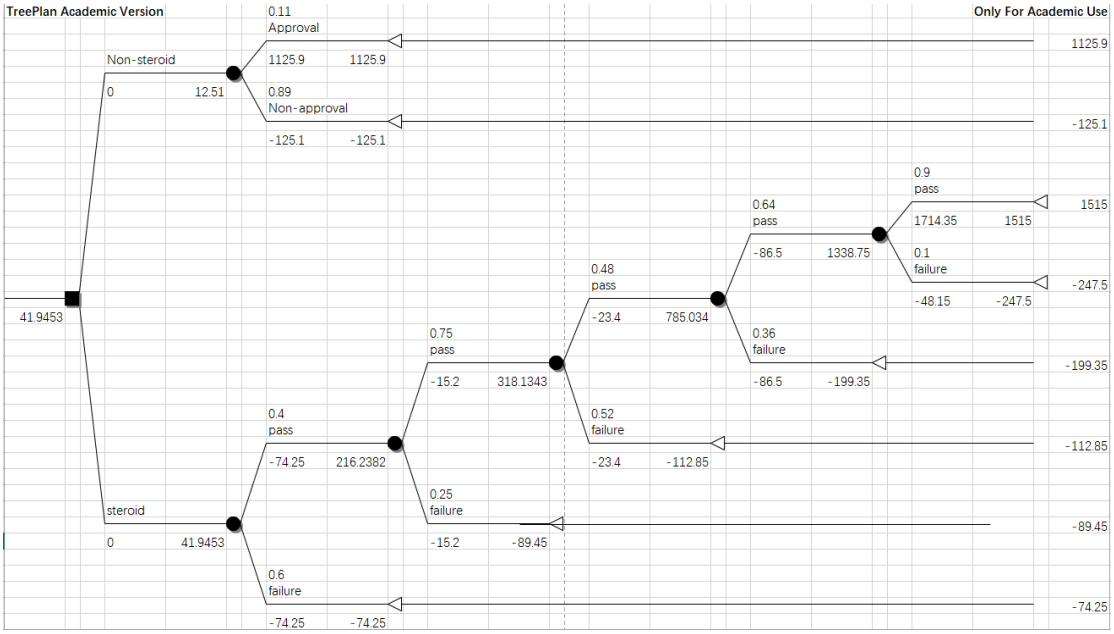
E(Steriod)= 12.51 < E(non-steroid pirfenidone)= 14.2315. Therefore, non-steroid pirfenidone has the higher expected value, so Marnac (Margolin) decided to pursue pirfenidone rather than the steroid。

2.2 Question 2

Assignment Questions pertaining to the revised Marnac decision using FDA average costs and probabilities from Table I and preceding paragraph:

Margolin utilizes the FDA average costs and probabilities by phase from Table I and preceding paragraph as well as his original estimated revenue ($1762.5M) and total cost ($247.5M). By so doing he replaces his estimate of 14.85% as the probability of FDA approval for pirfenidone.

1. Create the decision tree that represents a revised Marnac decision using FDA average costs and probabilities from Table I and preceding paragraph. It is straightforward except for the initial cost allocation of the "Investigational New Drug Application" (IND) and the final cost allocation of approval after all three phases had been approved (NDA) whose positions have been highlighted in yellow. As stated in the case, the former is 30% of the total cost or 30% of $247.5M, namely $74.25M while the latter is the difference of the total cost, $247.5M, minus all the prior allocations, namely $48.15M.



2. Viewing the tree, ask how many decisions for Marnac are represented? What are the risks Marnac faces?

There are 2 risks that they should faca.

For example,for non-steroids, the IND failed at the time of application; or for the first, second, and third stages, it failed; for steroids, the IND failed at the time of application.

3. Are there any ways in which Marnac can reduce its risk exposure? Could there be any additional decisions added to the tree? What might they be and where could they occur?

For non-steroids, they can be sold to company InterMune in the first stage;

For steroids, they can ask professional companies to investigate detailed data to get more targeted decisions.

The invention and creation of medicine is closely related to people's life and health. This requires inventors to grasp the best opportunity according to the process of research and development, and be ready to attack at one stroke.

They could repeat the procedures many times to improve drug accessibility and affordability Innovatively.

Yes,the first,second and forth one could added to the tree.

4. Why after Marnac passes Phase I, do you think Margolin decided to open discussions with InterMune concerning pirfenidone?

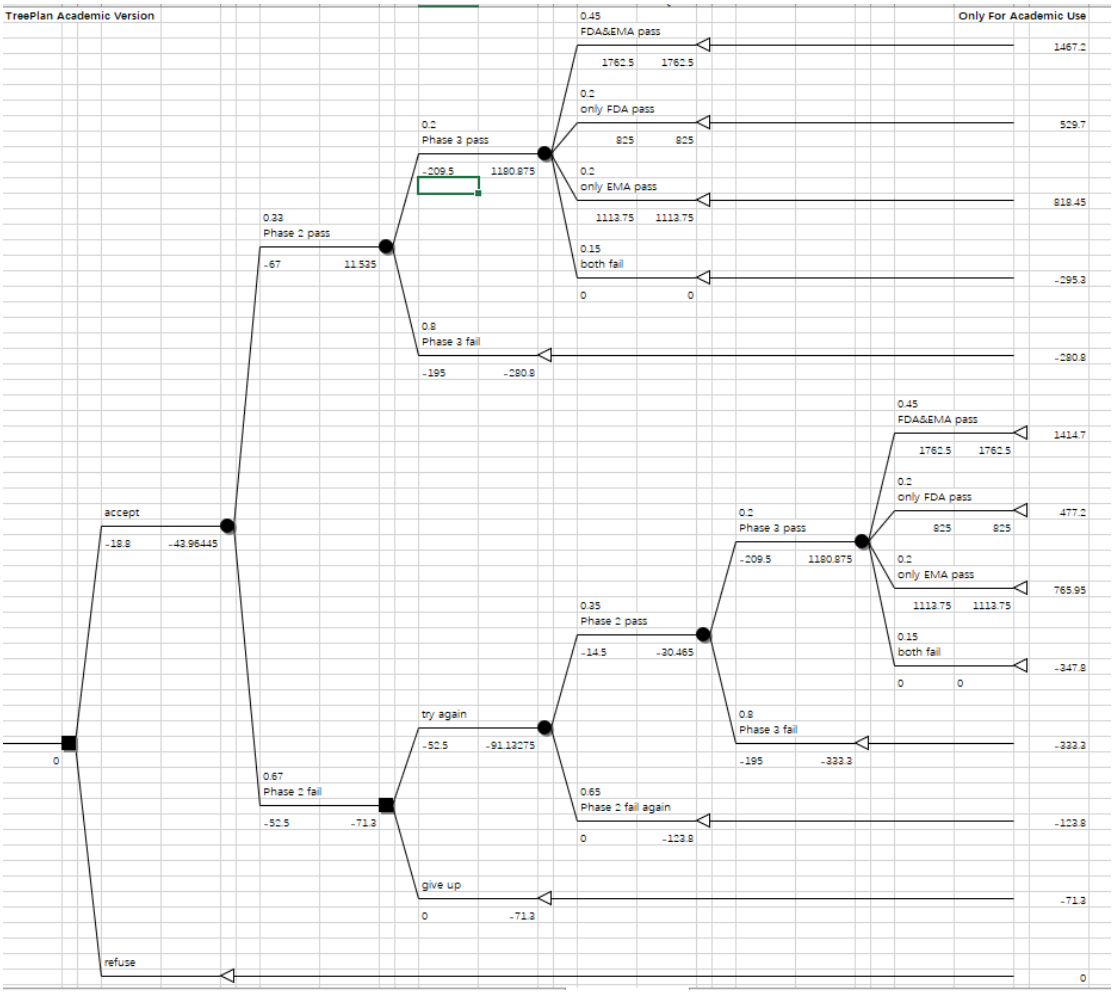
being a risk business person, Marnac believes that the probability of reporting from the second stage is high. After cooperating with company InterMune if the patent is sold to company InterMune ,the risk can be passed on to company InterMune at the same time.

2.3 Question 3

Assignment Questions pertaining to InterMune's point of view

InterMune Decision Milestone costs always incurred	
Case Facts	**Amounts in Millions$**
Upfront cost	-18.8
Milestone cost	-14.5
PII cost	-52.5
PIII cost	-195
US only Rev	825
Euro only Rev	1113.75
Both Rev	1762.5
Prob PII success	33%
Prob PIII success	20%
Prob PII Retry addl	2%

1. Build a decision tree that shows the cash flows and probabilities at all stages of InterMune's decision process for deciding whether or not to license pirfenidone.



2. Should InterMune bid to license pirfenidone?

they should not accept bids because when InterMune receive bids, his expected return is negative.

3. What is the recommendation regarding licensing pirfenidone that maximizes the expected value of the decision?

According to the decision tree，For InterMune, if it chooses to refuse the license，it will maximizes the expected value of the decision.

4. How much would InterMune expect to make doing so?

By refusing to accept license pirfenidone,InterMune do not lose money

5. How much would InterMune actually make doing so?

In fact, if InterMune companies accept license pirfenidone, their actual gains and losses are:

1467.2，529.7, 818.45，-295.3，-280.8, 1414.7, 477.2 , 765.95 ,-347.8 ,-333.3 ,-123,8 -71.3, 0

6. What risks does InterMune take on if they license pirfenidone?

For InterMune, if they choose to accept the license, they will start with a clinical trial phase of phase 2. Then InterMune company will face the following risks, clinical test stage two does not pass, stage three does not pass, only in the FDA, only in the EMA, in the FDA and EMA do not pass.

If they do not accept, there is no risk.

7. What is the probability that InterMune will lose money if they license pirfenidone?

According to the decision tree，if they license pirfenidone，the probability of losing money is 100%。

8. Why do you think Marnac and KDL were willing to have InterMune take over the FDA and European approval processes at Phase II?

Since Marnac and KDL are at risk when doing their own clinical tests, and the cost of the risk is higher than the cost of outsourcing, they want InterMune to accept phase two clinical tests.

2.4 Question 4

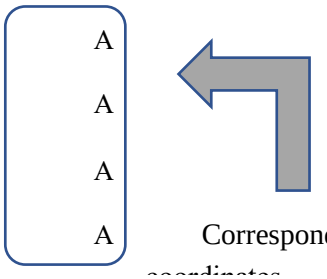
Assignment Questions pertaining to Sensitivity Analysis of InterMune's point of view:

1. InterMune is satisfied with the current ratios among the probabilities emanating from each chance node and would like to keep them aligned by selecting only the top-most probability from each chance node as a value to wiggle to reflect any uncertainty. Replace all the probabilities except the top-most from each chance node with their corresponding equations to ensure the ratios among the probabilities emanating from each chance node remain and use the bottom-most probability to ensure that the sum of the probabilities from each chance node is 1.

1)Use the formula function of Excel: making the probability equal to the value of the specified cell coordinates.

Next, take the probability of passing stage 3 as an example

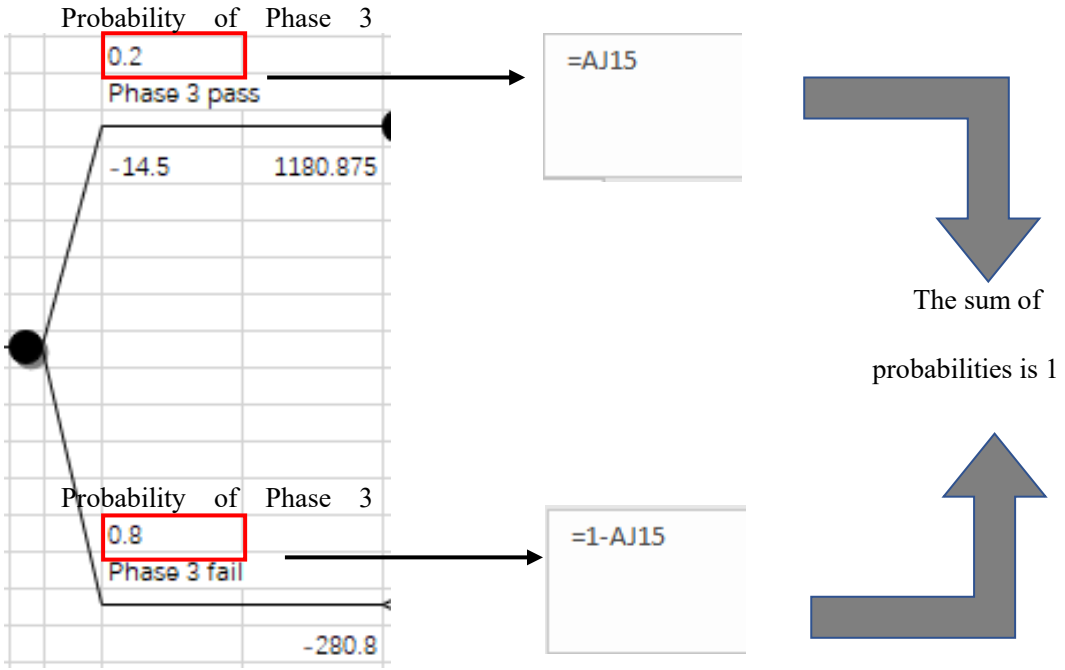
①Create a table of cells and indicate the corresponding meaning



Corresponding cell coordinates

the cost of Phase 3	195
The probability of the phase 3 pass	0.2
The probability of the phase 2 pass	0.33
The probability of the phase 2 retrial pass	0.35

② Replace all the probabilities with their corresponding equations



③Change the value of cell, and observe the change of expectation

$$f(x) = ax + b$$

Because the final formula must be linear, we can substitute two sets of different data to get multiple points, and then deduce the formula

2) Through formula method, express the formula of expectation profit about probability

$$Ex(E_k / D_k) = \sum P_i Ex(E_i / D_i)$$

$$Ex(E_k / D_k) = Max\{E_i, E_{i+1} \ldots\}$$

where E_i / D_i is the branch of E_i / D_i

Starting from the far right of the decision tree and iterating to the left, we can finally get the expectation of decision making with probability

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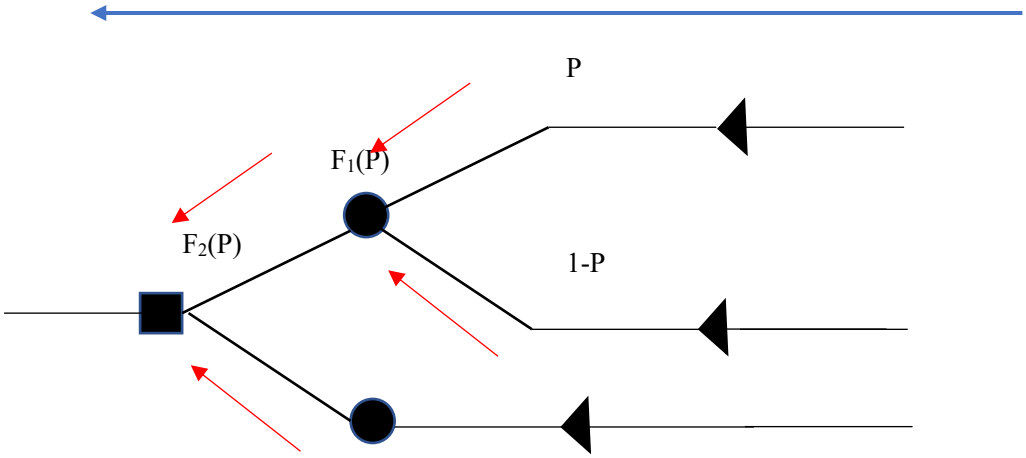
From right to left



2. If the cost of Phase III testing of pirfenidone could be as low as $100 million to even as much as a $1 billion, would your recommendation on InterMune's licensing of pirfenidone change? Why or why not?

Let the cost of phase 3 be C, and put it into the decision tree to calculate the expectation of accepting authorization, we can get:

$$Ex(E_2) = 167.535 - 0.8C$$

$$Ex(D_2) = Max\{-71.3,\ 36.5328 - 0.28C\}$$

$$Ex(E_1) = 0.33Ex(E_2) + 0.67Ex(D_2)$$

$$Ex(E_1) = \begin{cases} 79.763526 - 0.4516C & 124.16857 < C < 1000 \\ 7.51555 - 0.264C & 100 < C \le 124.16857 \end{cases}$$

3. Suppose the probability of successfully passing Phase III in the US only is uncertain but believed to be between 10% and 22%. What should InterMune do?

Let the probability of the phase 3 passing be P_1, and put it into the decision tree to calculate the expectation of accepting authorization, we can get:

$$Ex(E_1) = -140.435 + 482.3528P_1,\ 10\% < P_1 < 22\%$$

4. Suppose the probability of successfully passing Phase II and entering Phase III is uncertain

but believed to be between 1% and 40%. Would that change your insight?

Let the probability of the phase 2 passing be P_2, and put it into the decision tree to calculate the expectation of accepting authorization, we can get:

$$Ex(E_1) = -71.3 + 82.835P_2,\ 1\% < P_2 < 40\%$$

5. Instead of the probability of success being slightly greater than 33% if the initial Phase II results were insufficient to pass and InterMune decides to conduct a retrial, suppose it could be as low as only 5% or as high as 40%. What should InterMune do?

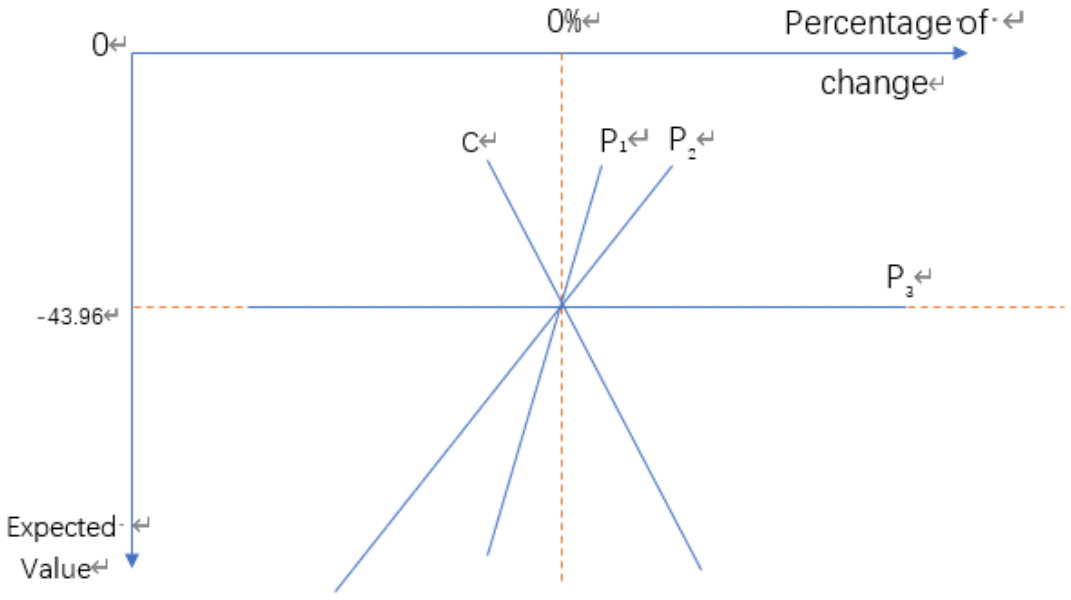
Let the probability of the phase 2 retrial passing be P_3, and put it into the decision tree to calculate the expectation of accepting authorization, we can get:

$$Ex(E_1) = -43.96445,\ 5\% < P_3 < 40\%$$

6. Which of the ranges of uncertainties as described in the four prior questions have the biggest impact on the Expected Value?

Draw the image of the percentage of parameter change -- expected profit.

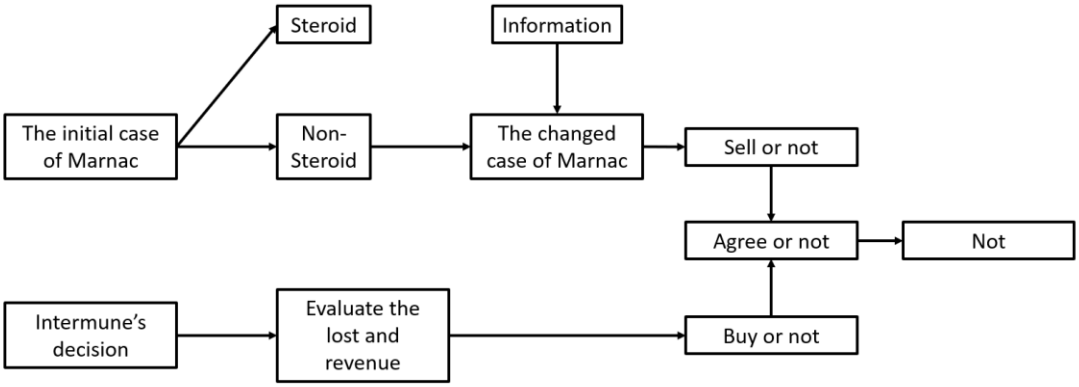
According to the slope, P1: the probability of the phase 3 passing has the biggest impact on the Expected Value.



7. Which of these ranges of uncertainty should InterMune try to reduce? Why? What techniques might they use to do so?

Intermune should try to reduce the range of C, P1, P2 in uncertainty, because they have a significant impact on expected value. To do this, we can do relative research study, survey, sampling, product testing, etc

3. Summary


Steroid
Information
The initial case of Marnac
Non-Steroid
The changed case of Marnac
Sell or not
Agree or not
Not
Intermune's decision
Evaluate the lost and revenue
Buy or not