Clinical Creations

Cartilage Tissue Engineering

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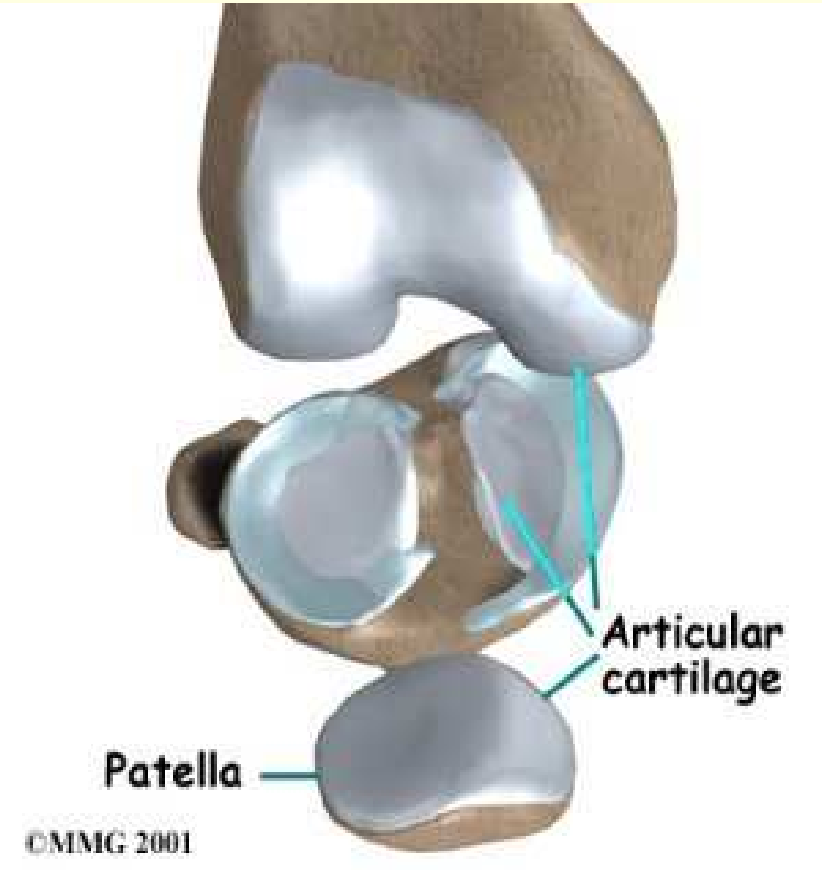
Overview

- Cartilage damage in the knee is a major problem
- We present a novel tissue engineering technique for repairing cartilage damage with autologous chondrocyte cells
- Mathematical modeling can be useful to help predict implant behavior
- The FDA approval process and product pricing were modeled in order to evaluate risk

Cartilage



Ref: football.calsci.com/ images/knee_cartilage.jpg

- Connective tissue found in all joints
- Functions as cushioning and support
- Cartilage is composed of chondrocytes, collagen, and proteoglycans.
- Articular cartilage is found in the knee joint.
  - Strongest type of cartilage

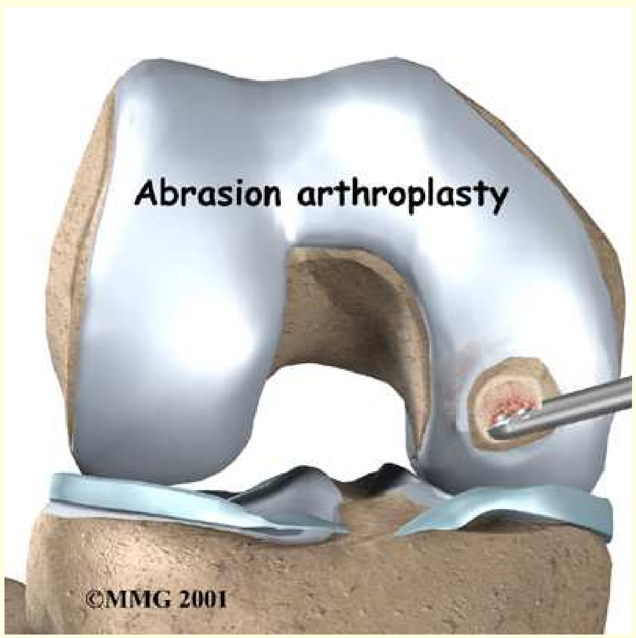
Cartilage Damage

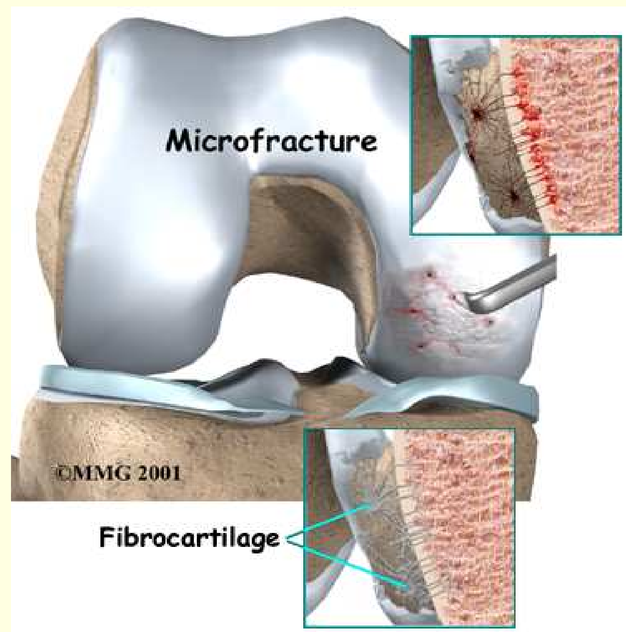
- Tears and holes develop in cartilage due to injury and stress.
- No vascular system is present throughout the cartilage to initiate repair after damage.
- Damage develops in cartilage and extends into the underlying bone.

http://www.orthogastonia.com/index.php/fuseaction/patient_ed.topicdetail/TopicID/a93dd54cd3d79c0d8bedae1537bc7659/area/17

Reparative Surgeries

- Inflict further damage to initiate the healing response.
  - New tissue does not have the required mechanical strength.
  - Results are temporary.





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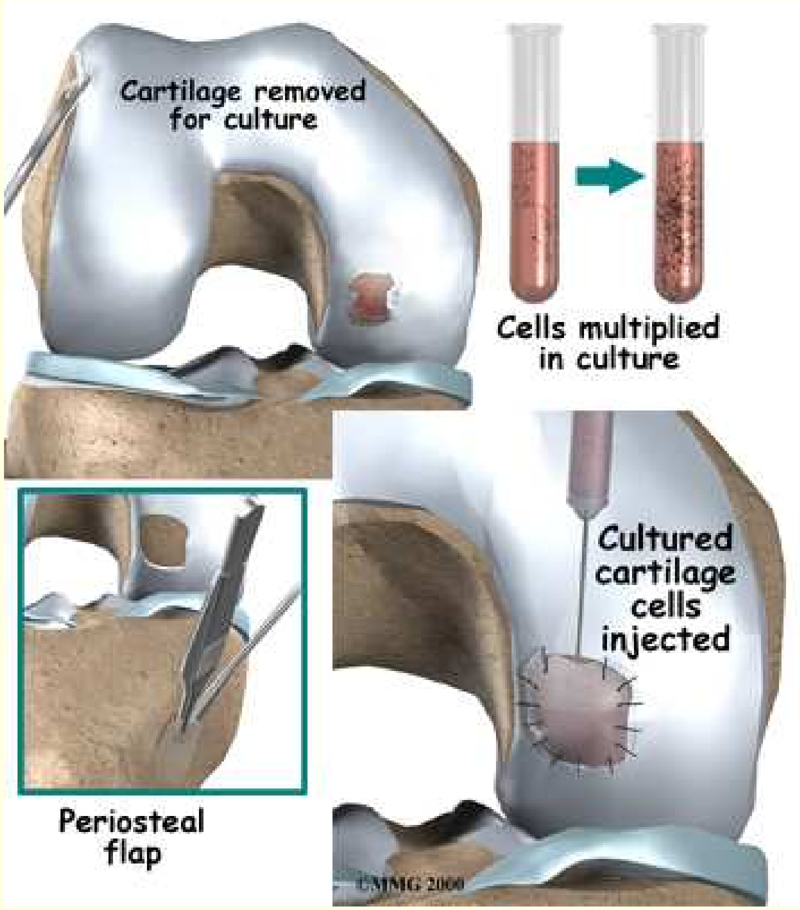
Restorative Surgeries

- Replace cartilage with cells or donor tissue.
  - Invasive
  - Lack reliability
  - High risk of initiating an immune response
  - Cells migrate from damage site



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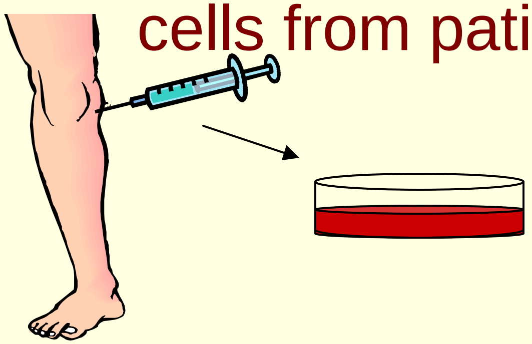
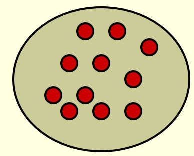
Our Solution

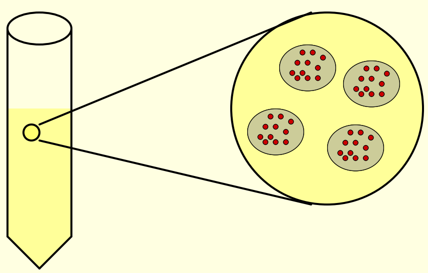
1) Harvest and proliferate cells from patient



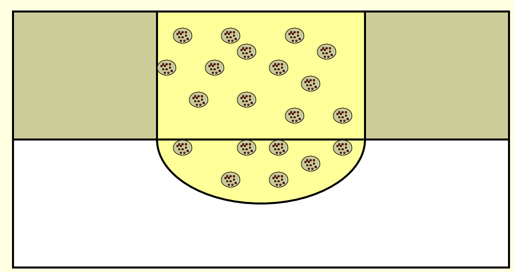
2) Embed cells in gelatin microcapsules



3) Suspend capsules in crosslinkable polymer



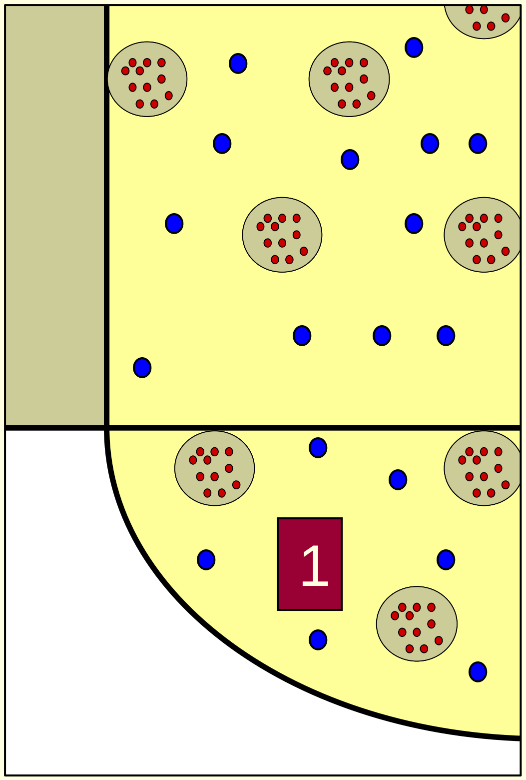
4) Inject polymer into defect and crosslink *in situ*



After crosslinking, microcapsules will release cells. Over time, polymer will degrade and cells will produce new tissue

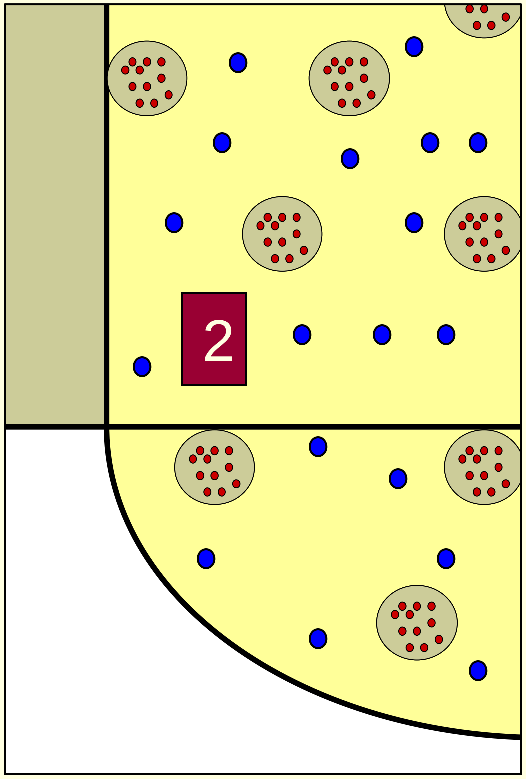
Cartilage Repair

1. Bone replacement:
   - Made of poly(propylene fumarate) (PPF) combined with β-TCP particles
   - Seeded with mesenchymal stem cells taken from the patient's bone marrow.
   - N-vinylpyrrolidinone serves as a crosslink and benzoyl peroxide initiates crosslinking upon injection



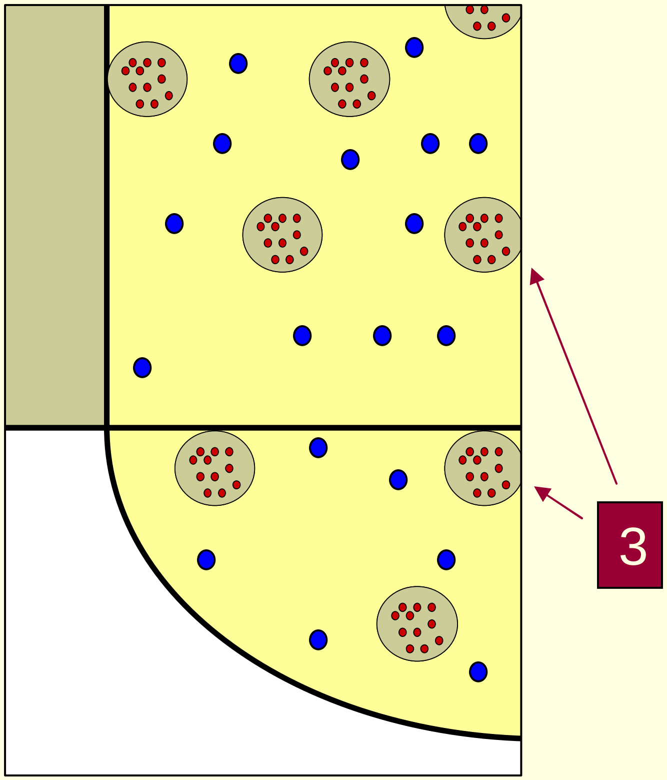
Cartilage Repair

2. Cartilage Replacement:
   - Made of a copolymer containing PPF and poly(ethylene glycol) (PPF-co-EG)
   - Seeded with chondrocytes taken from a non-load bearing joint
   - Undergoes the same crosslinking reaction as the bone replacement



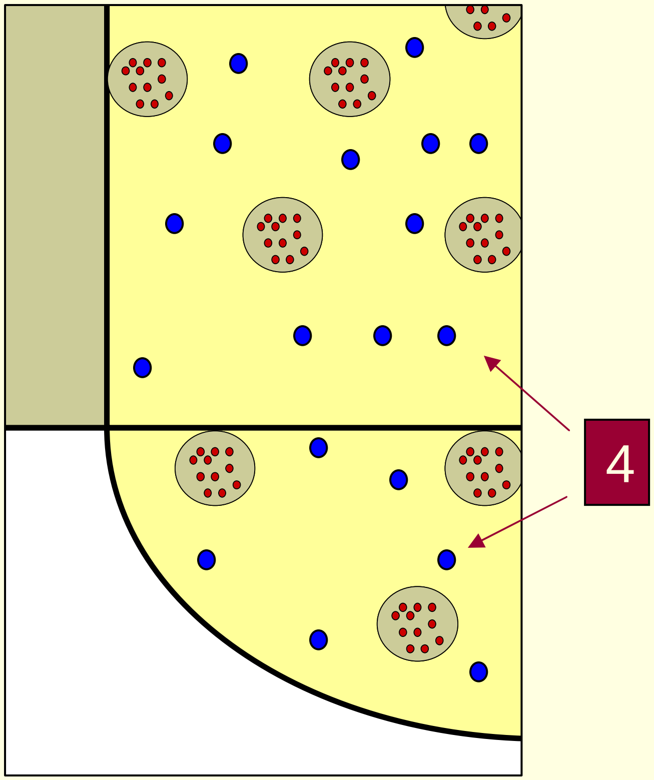
Cartilage Repair

3. Cell Microcapsules
   - Microcapsules will contain porcine gelatin and DMEM cell culture media
   - Surface will be crosslinked using DSP to prevent reverse gelation of microparticles during PPF crosslinking



Cartilage Repair

4. Growth Factors
   - PLGA microparticles containing growth factors will also be suspended in the polymer
   - These will release growth factors slowly throughout tissue regeneration to promote cell growth and activity



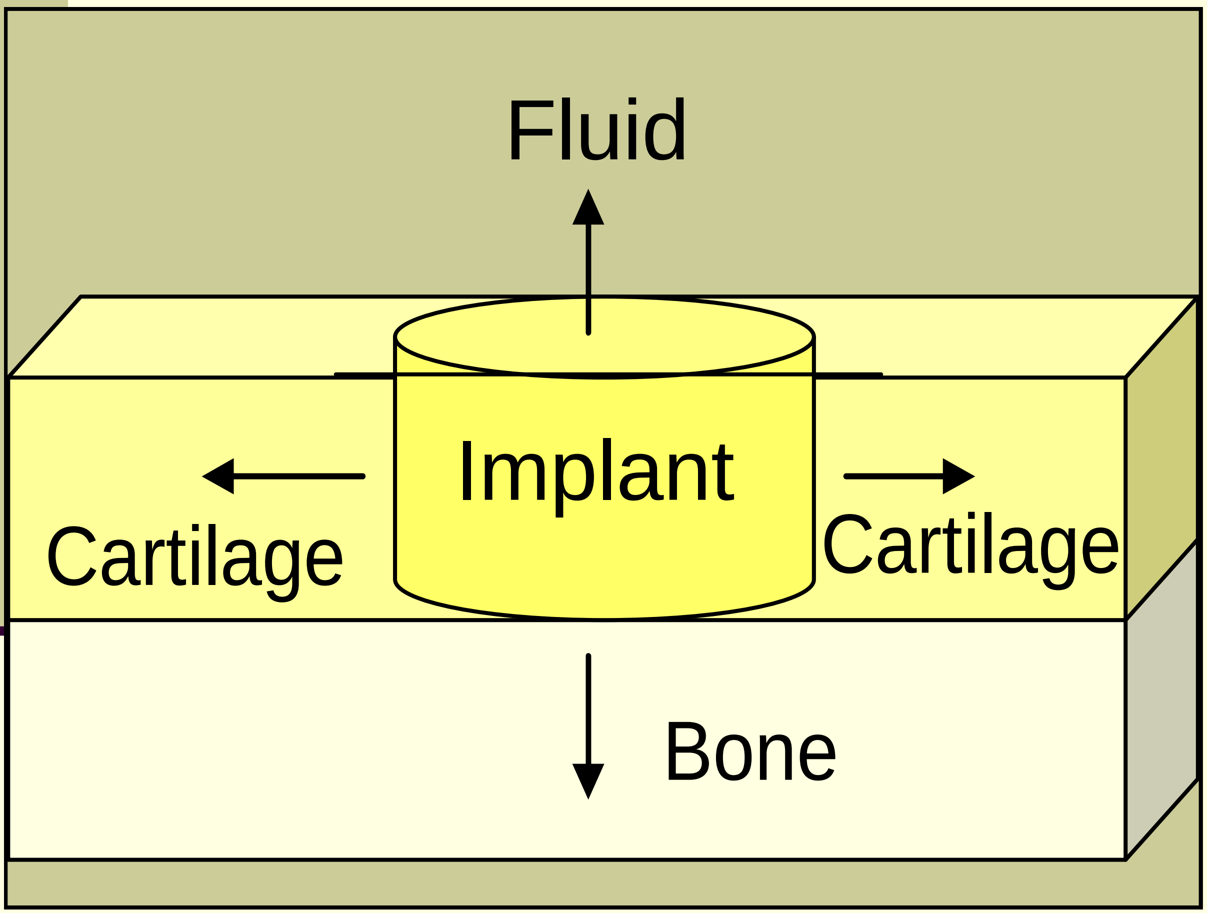
Technical Models

- Mathematical modeling of aspects of this procedure will decrease the amount of experimentation needed and decrease the risk associated with lack of knowledge.
- Aspects that can be modeled:
  - Heat Transfer
  - Mechanical Strength / Porosity
  - Polymer Degradation

Heat Transfer

- When cell suspension polymerizes *in vivo*, heat is produced.
- This causes the temperature of the polymer construct to increase.
- Excessive temperatures can kill the cells before they can begin to proliferate and create tissue.
- Will increased polymer temperatures allow enough cell survival for tissue growth?

Heat Transfer



Inside Implant

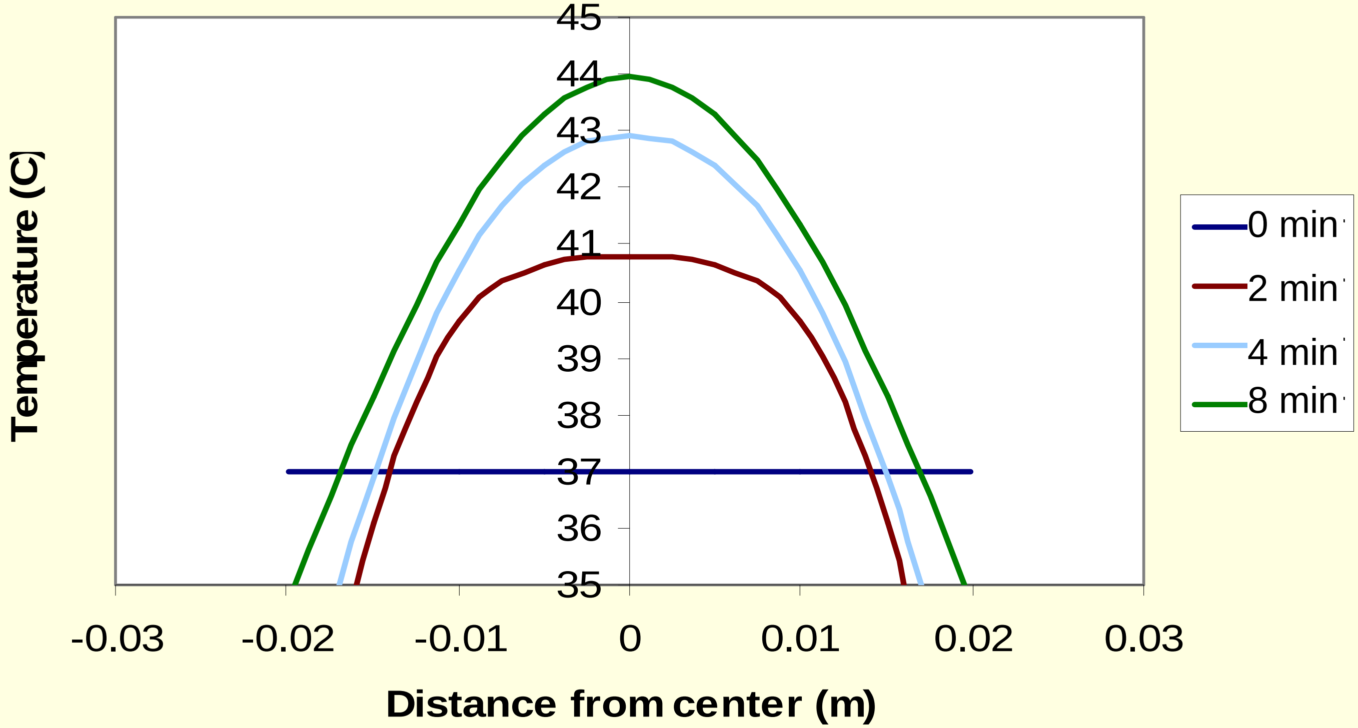
$$\alpha_1 \frac{\partial T}{\partial t} = \nabla^2 T + \dot{q}(t)$$

Outside Implant

$$\alpha_2 \frac{\partial T}{\partial t} = \nabla^2 T$$

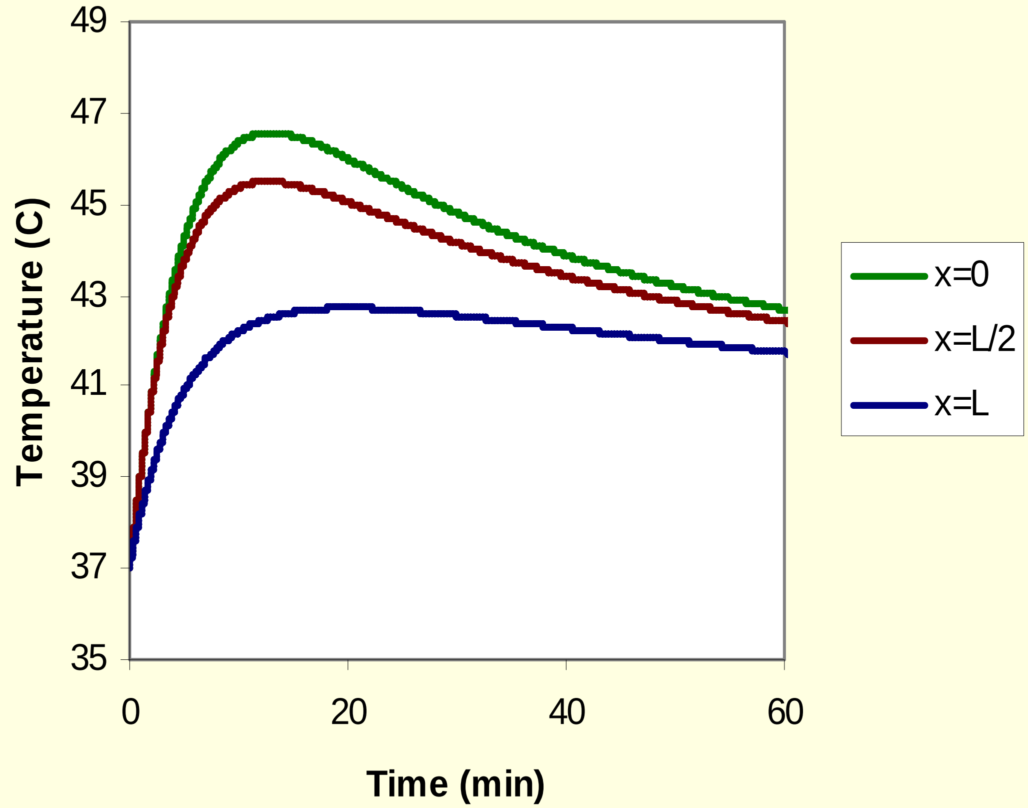
Heat Transfer

- First attempt: 1-D Analytical Solution
- Solution of inner equation is not consistent with boundary conditions.



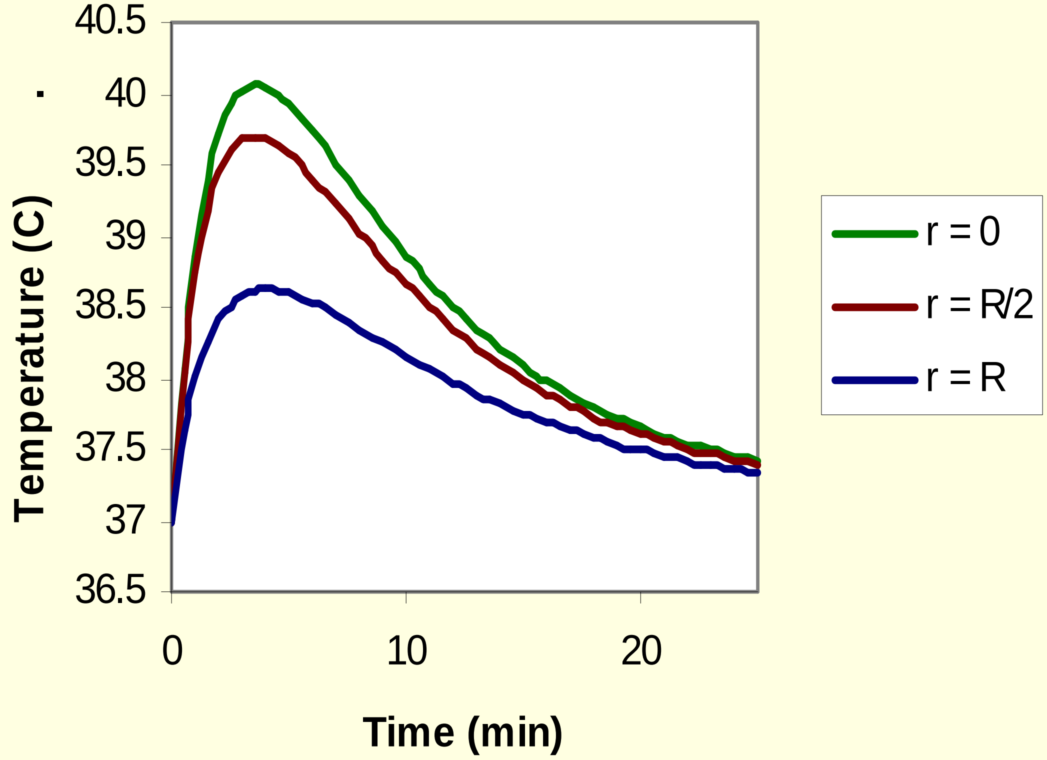
Heat Transfer

- Second Attempt: find 1-D solution numerically using finite differences
- Temperature raises to almost 47ºC and stays above 40ºC for several hours
- This would cause significant cell death



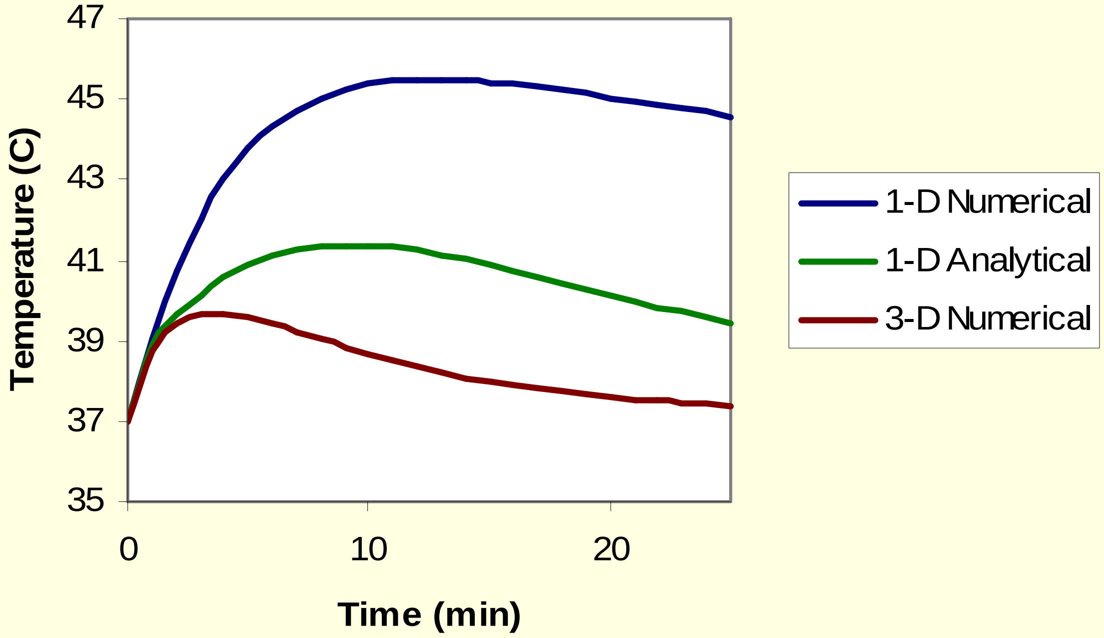
Heat Transfer

- Third Attempt: Find 3-D solution in cylindrical coordinates using finite differences
- Temperature only increases to 40 C at the Center of the Implant
- This temperature increase will cause minimal cell death



Heat Transfer

- Comparison between methods
- 1-D Models do not consider heat lost through the top and bottom of the implant



Heat Transfer

- Model shows that temperature increase will not cause significant cell death.
- This prediction gives a starting point for experiments in cell seeding.
- The model saves us money and time that would otherwise be used to find these results experimentally

Mechanical Strength

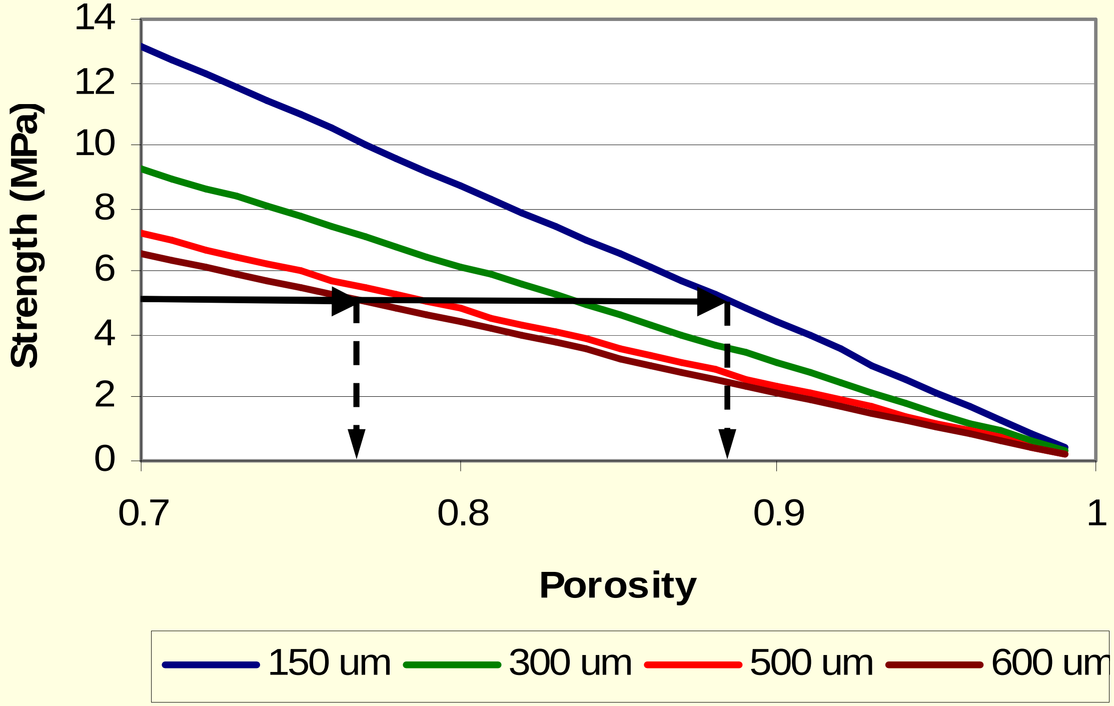
- Proper mechanical strength will allow for better recovery for the patient
- Natural compressive strength
  - Bone ~ 5 MPa
  - Cartilage ~ 0.4 – 1.4 MPa
- Variables affecting construct strength throughout device life:
  - Cross-linking density
  - Porosity
  - Degradation and cell growth

Porosity

- Void space is necessary to create pathways for nutrient and waste movement.
- Porosity affects compressive strength of the material
  - Percent porosity of material
  - Size and morphology of pores
- Atzeni equation developed for hardened pastes with spherical pores.
  - Empirical constant is necessary

$$\sigma = K\frac{\sigma_0(1-p)}{\sqrt{r_m}}$$

PPF/β-TCP Porosity



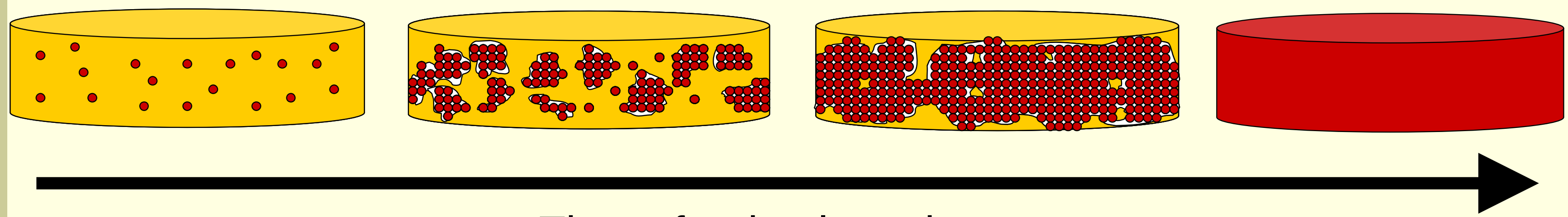
$$\sigma = 4.3\frac{\sigma_0(1-p)}{\sqrt{r_m}}$$

- Natural bone has a compressive strength of 5 MPa.
- Bone substitute could have a porosity over 75% based on this model.

PPF-co-EG Porosity

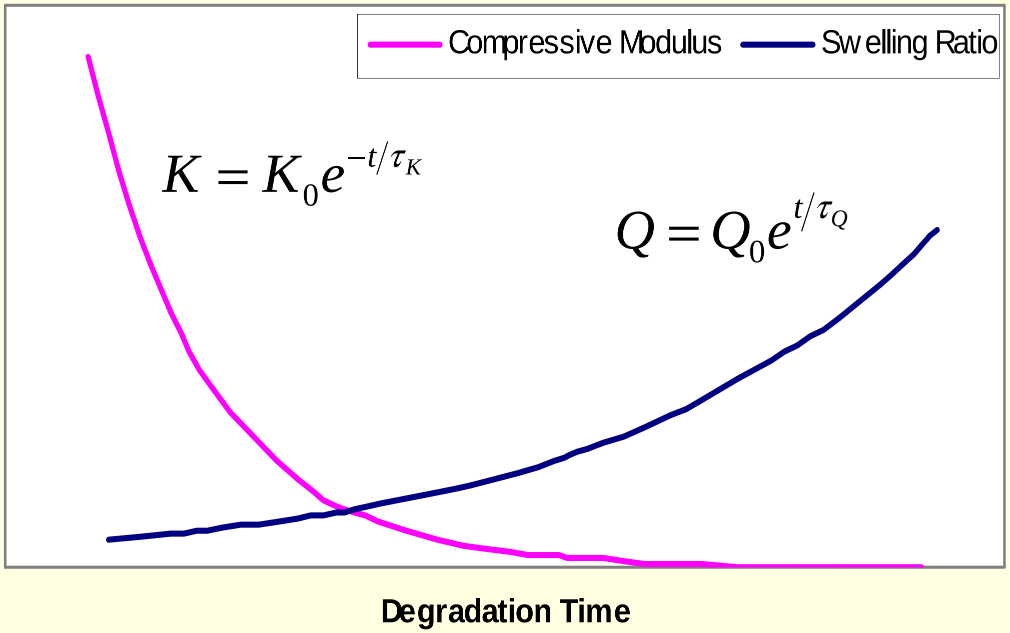
- Polymer matrix forms a hydrogel, which has natural void space.
  - Dependent on cross-linking density
- Shown to have adequate diffusion of nutrients, waste, and large proteins.
- Diffusion of nutrients and mechanical strength are affected by the cross-linking density of the polymer.

Construct degradation



- Degradation occurs by hydrolysis of PPF bonds.
- Pseudo-first order kinetics because water concentration is relatively constant.
- Degradation decreases cross-linking density
  - Decreases compressive strength
  - Increases swelling ratio

Degradation Effects



- As degradation increases, polymer loses strength
- Degradation rate is dependent on initial cross-linking density
- Cell growth must replace degraded polymer to maintain strength.

Modeling

- We now have a better idea of which experiments must be done in order to make this process work.
- Overall, numerical models like this help to reduce cost and more accurately quantify risk…

Risk Analysis

Need for Risk Analysis

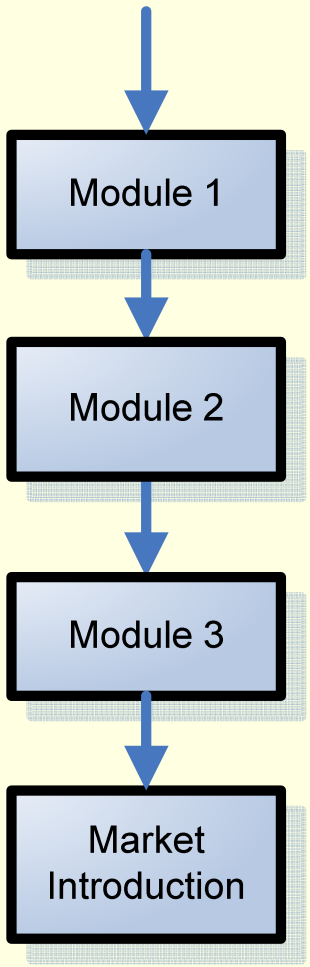
- New technologies include an incredible amount of risk
  - 5 of every 5,000 medical technologies that enters the FDA approval process enters human clinical testing.
  - Only 1 of those 5 technologies will eventually be approved for the medical market.
- On average, it takes 15 years for the approval process.
- It takes approximately $360 million for a new technology to reach the public.

FDA Approval

- Necessary before the use of any medical device.
- Experiments determine the positive and negative affects of the treatment.
  - Lab scale testing
  - Animal testing
  - Human clinical trials
- Application can be filed in a traditional or modular form.

Modular FDA Approval

- Modules are determined based on assessment of needed experiments.
- Request approval at the end of each module
- Failure within a module does not indicate total product failure
  - Data appendices can be sent in after approval was requested.
- Project can be abandoned after failure at any module.



FDA Approval

- Module 1 – Laboratory testing
  - Bench scale testing
  - Basic material properties
  - Initial optimization of construct
- Module 2 – Non-clinical animal studies
  - Defining surgical procedure
  - Biocompatibility and toxicity studies
  - Further optimization of construct
- Module 3 – Human clinical trials
  - Mechanical strength and integrity
  - Long-term *in vivo* results

Assessing Pathways

- Each step has an associated time, cost, and probability.
- To assess the FDA process, estimations of where failures will occur must be made.
- Number of failures allowable within a pathway will greatly affect the risk assessment.
- Probabilities of success would increase if
  - Pre-FDA testing is completed
  - More experiments are performed
  - Advance and accurate modeling is available

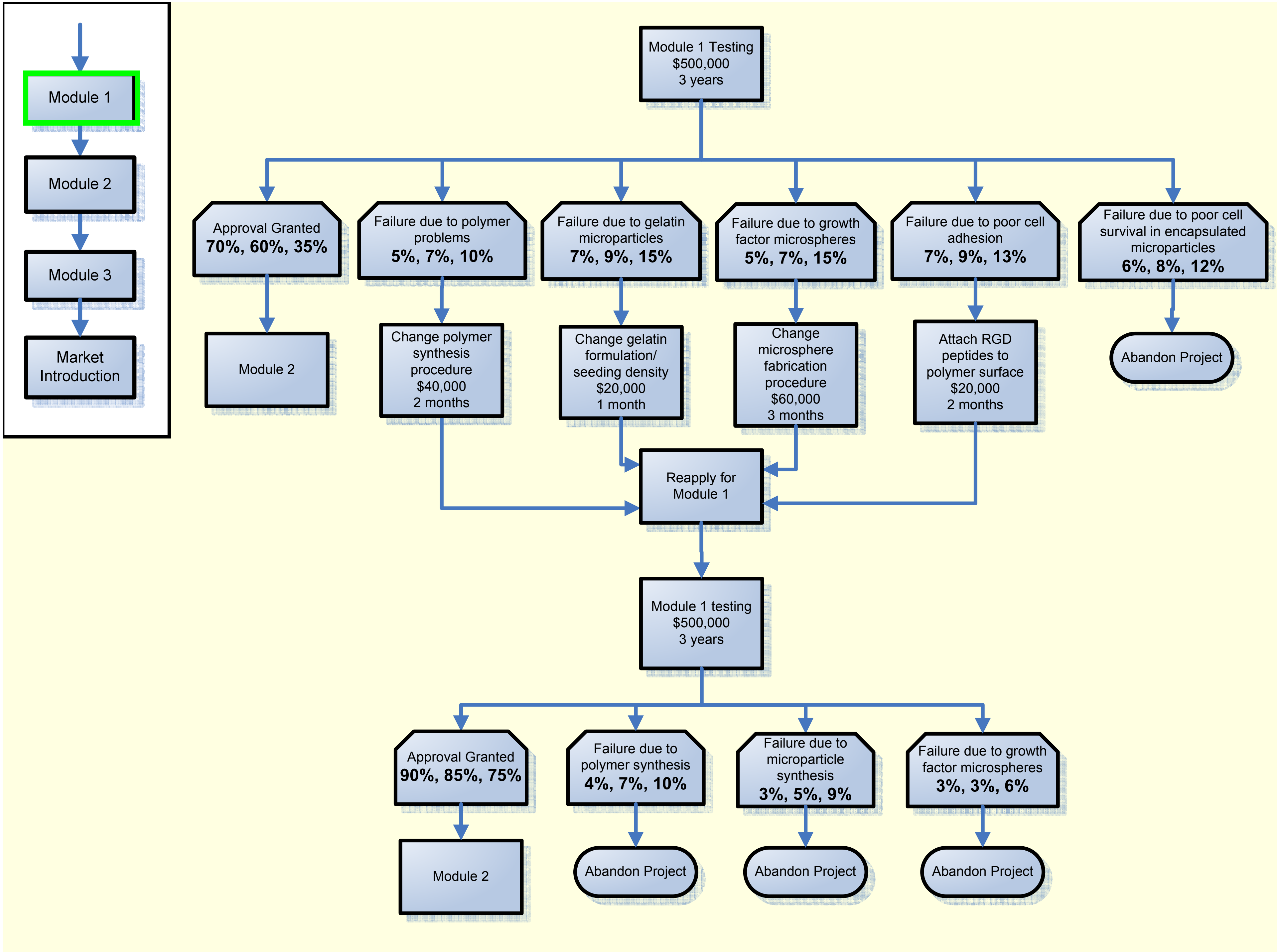
Pre-FDA Trials

- Reduces the chance of early failure
- Abandon or change project based on results
- Predict necessity of more expensive experiments and optimizations
- Increases accuracy of risk analysis

Business Decisions

First Stage Decisions:	Second Stage Decisions:
Number of experiments	Product price
Number of workers	Advertising Costs
Number of Allowable Failures	Production facility location and size

- We will find risk associated with several first stage scenarios – it is assumed that second stage decisions can be made later for optimum performance



Module 1
Module 2
Module 3
Market Introduction
Module 1 Testing
$500,000
3 years
Approval Granted
70%, 60%, 35%
Failure due to polymer problems
5%, 7%, 10%
Failure due to gelatin microparticles
7%, 9%, 15%
Failure due to growth factor microspheres
5%, 7%, 15%
Failure due to poor cell adhesion
7%, 9%, 13%
Failure due to poor cell survival in encapsulated microparticles
6%, 8%, 12%
Module 2
Change polymer synthesis procedure
$40,000
2 months
Change gelatin formulation/ seeding density
$20,000
1 month
Change microsphere fabrication procedure
$60,000
3 months
Attach RGD peptides to polymer surface
$20,000
2 months
Abandon Project
Reapply for Module 1
Module 1 testing
$500,000
3 years
Approval Granted
90%, 85%, 75%
Failure due to polymer synthesis
4%, 7%, 10%
Failure due to microparticle synthesis
3%, 5%, 9%
Failure due to growth factor microspheres
3%, 3%, 6%
Module 2
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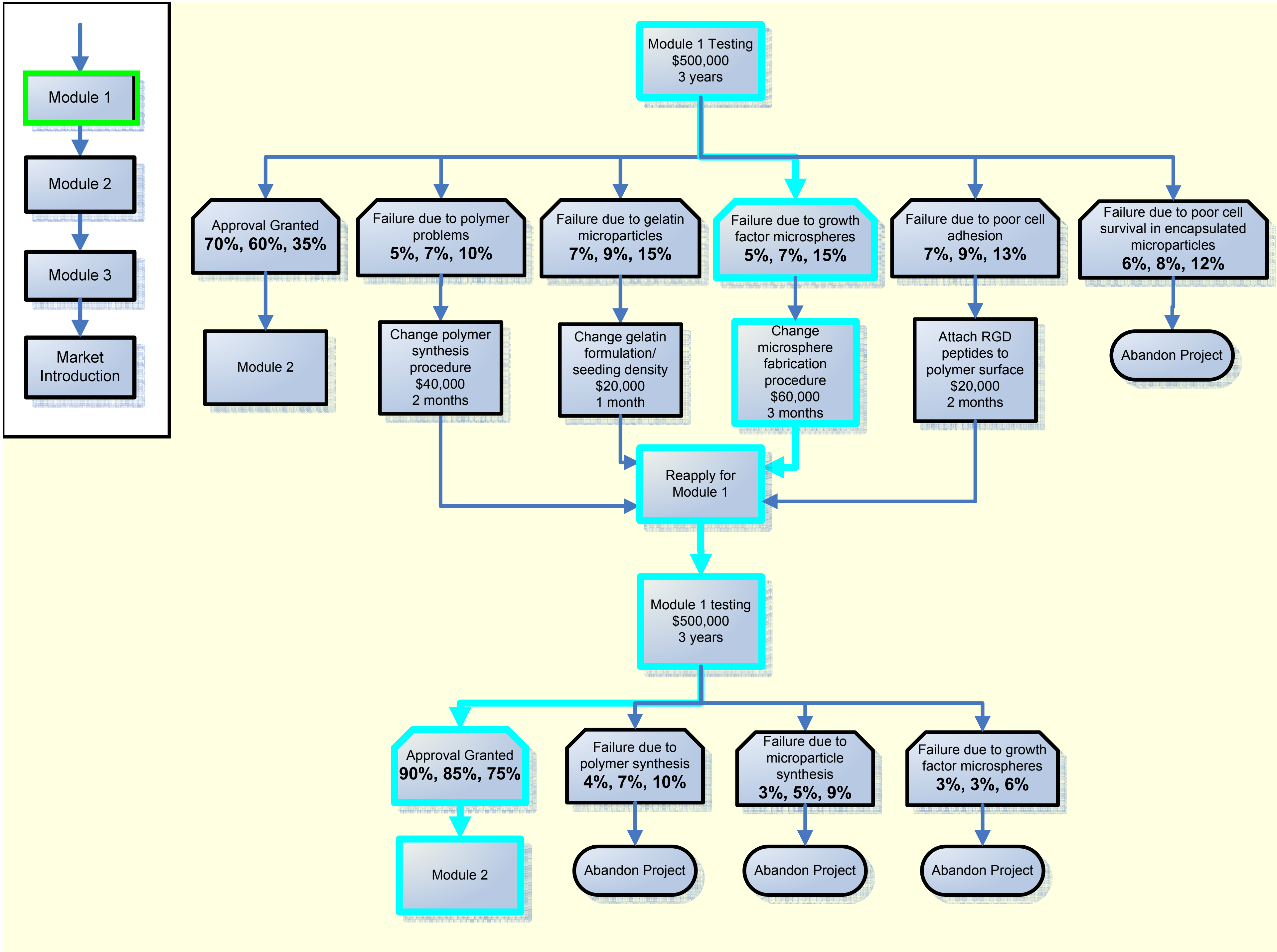
Abandon Project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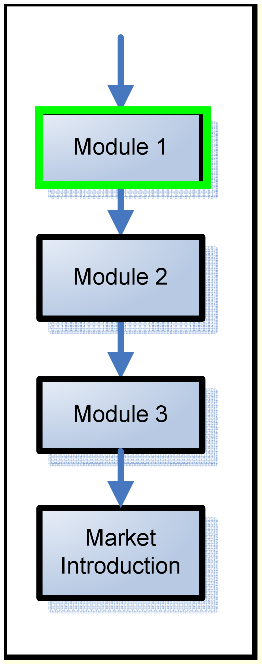
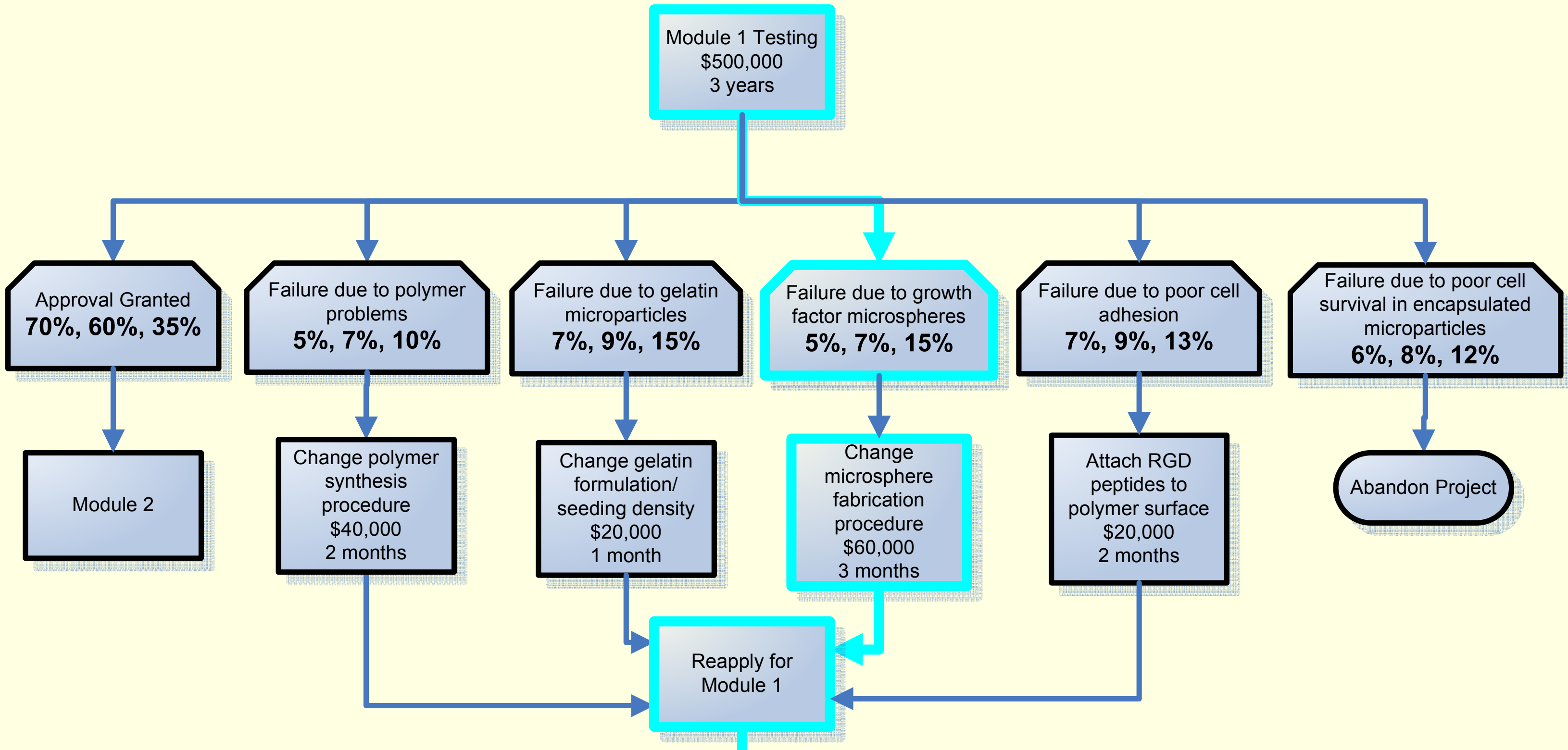
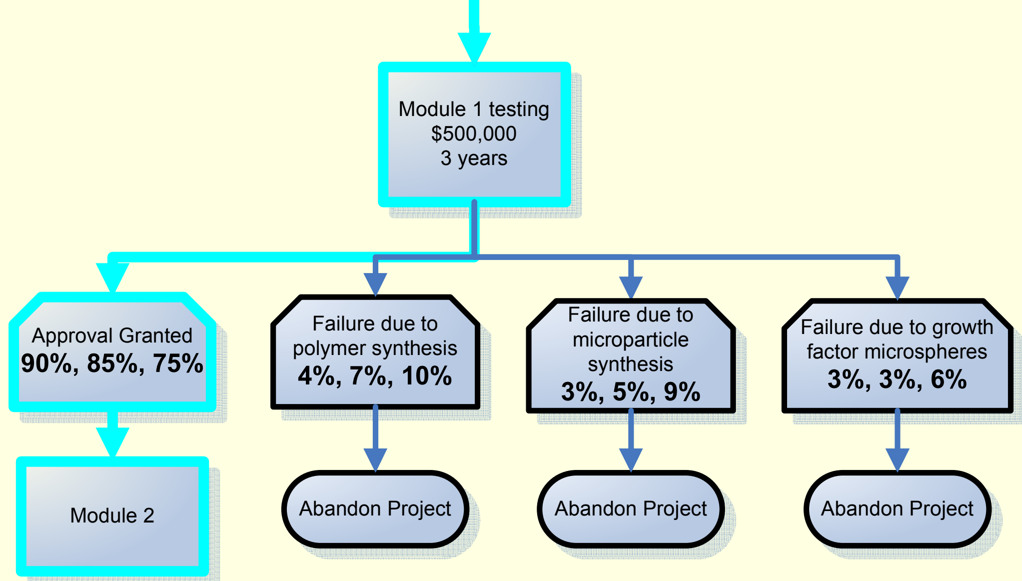






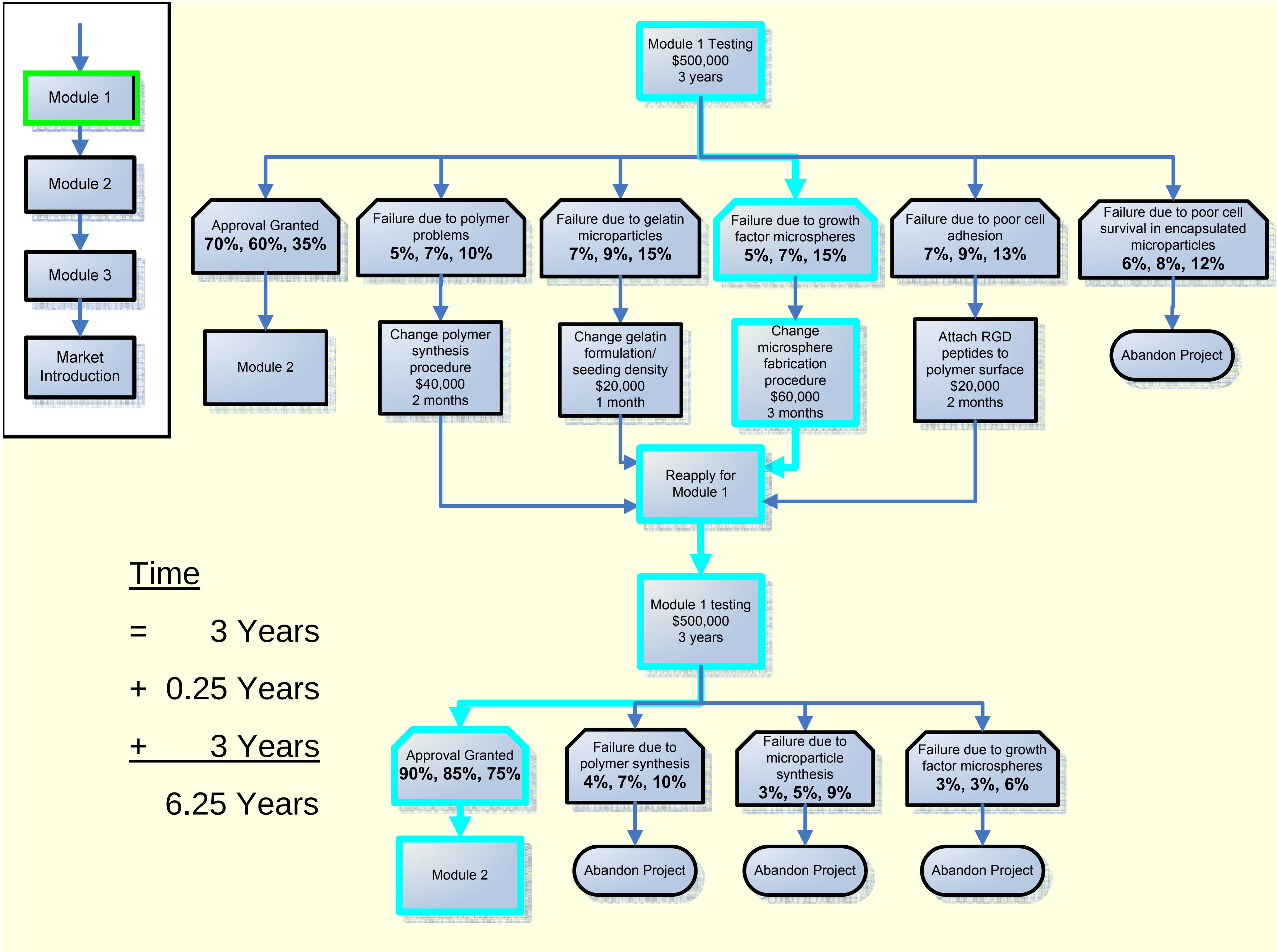
<u>Cost</u>

= $500,000

+ $60,000

<u>+ $500,000</u>

$1,060,000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Time
= 3 Years
+ 0.25 Years
+ 3 Years
6.25 Years
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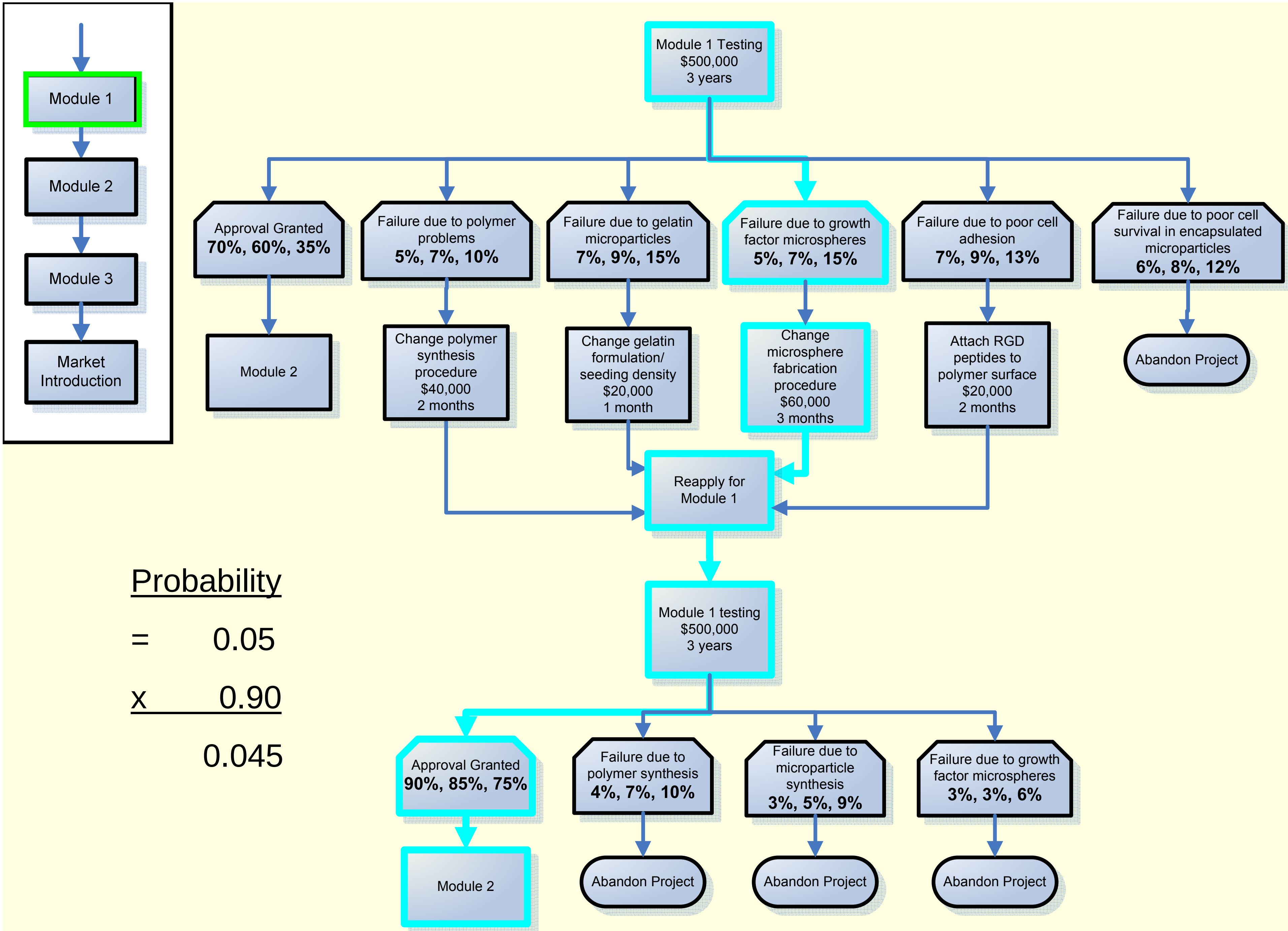
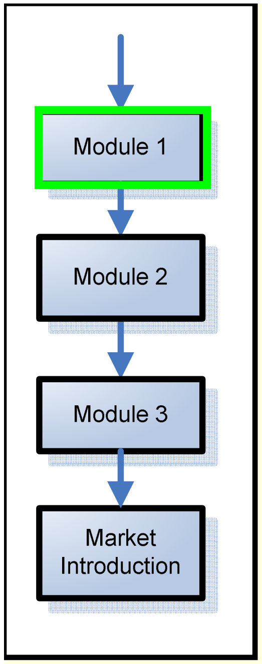


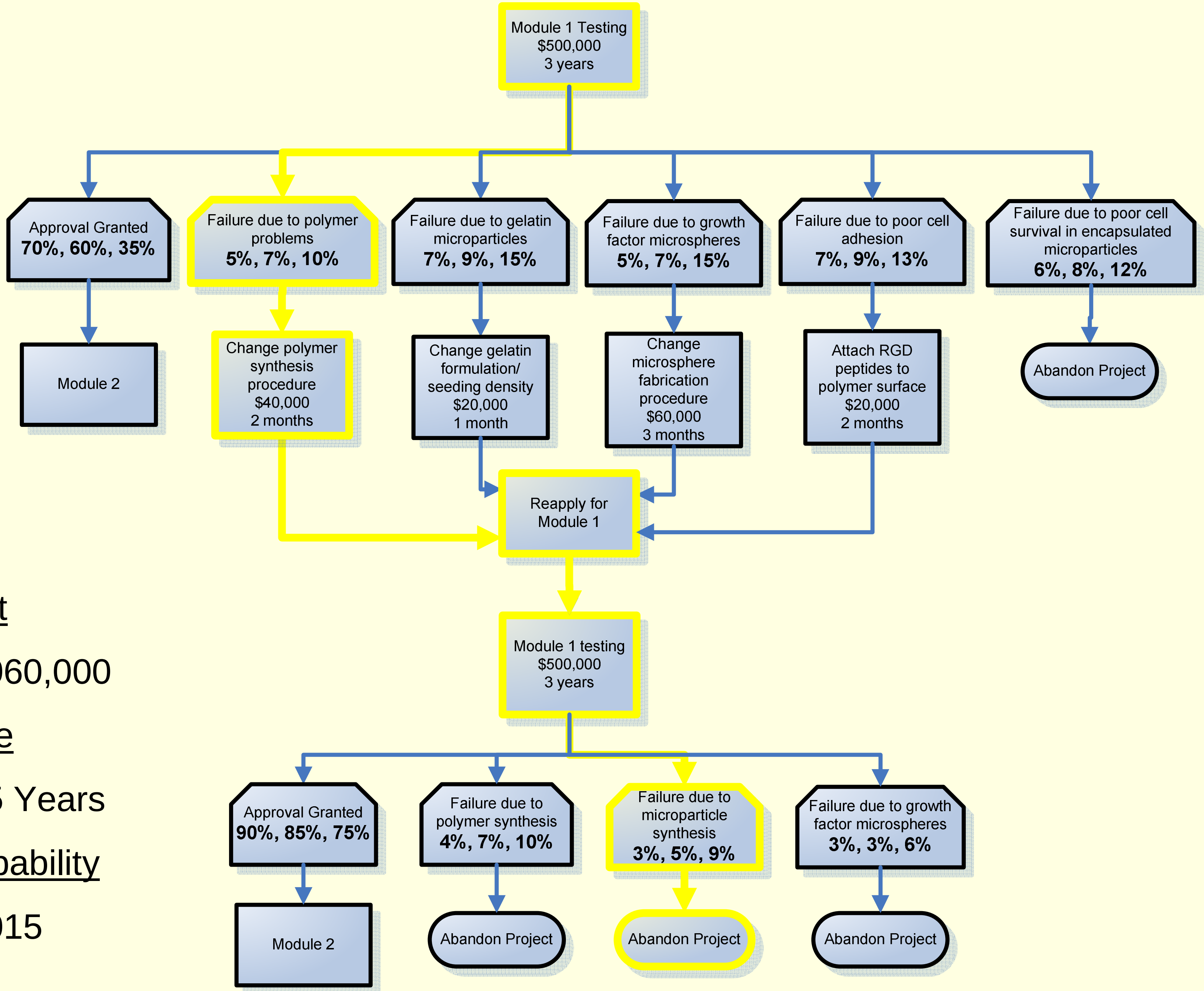
Probability

= 0.05

x 0.90

0.045





Cost

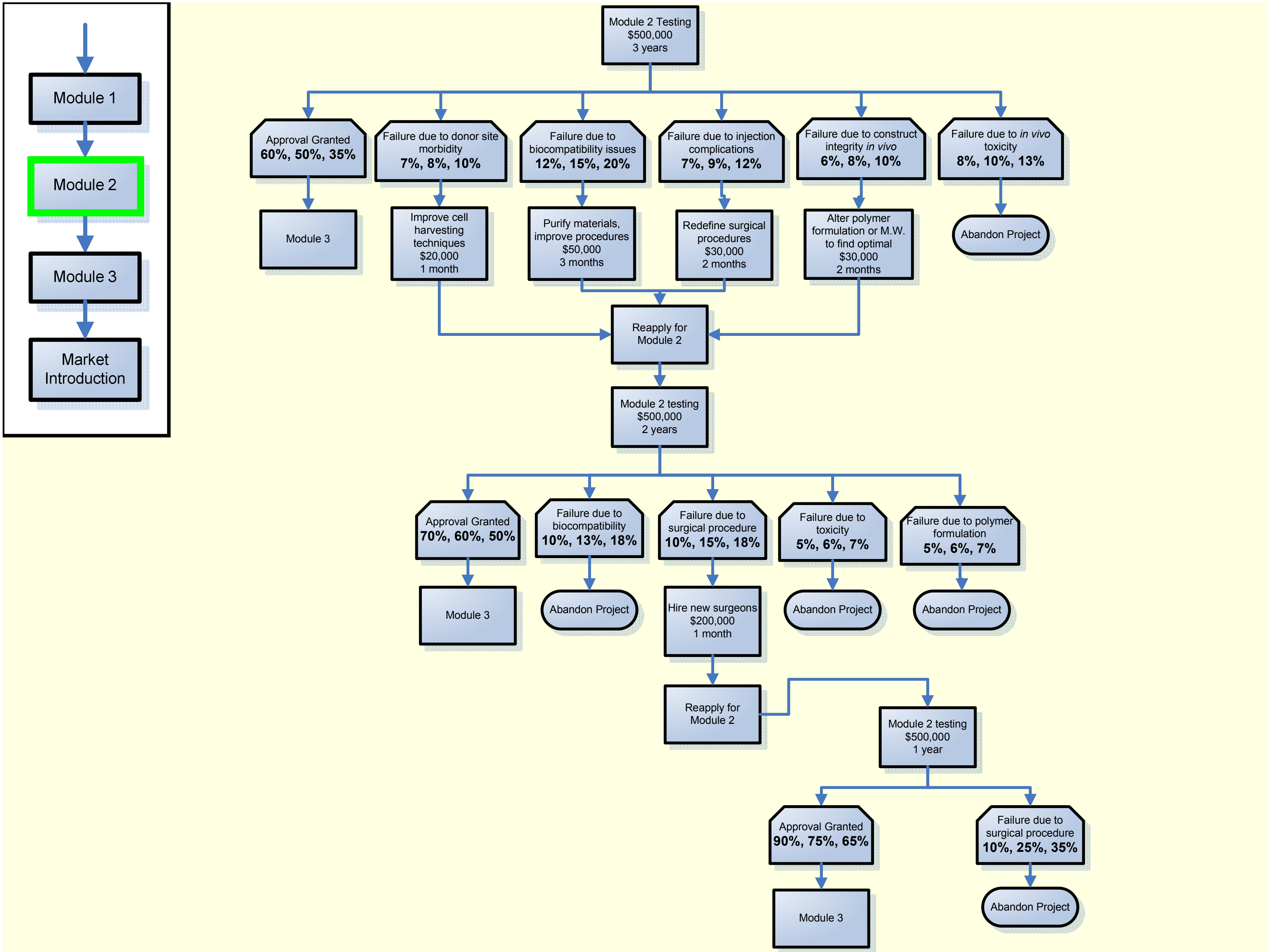
$1,060,000

Time

6.25 Years

Probability

0.0015



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Improve cell harvesting techniques $20,000 1 month
Purify materials, improve procedures $50,000 3 months
Redefine surgical procedures $30,000 2 months
Alter polymer formulation or M.W. to find optimal $30,000 2 months
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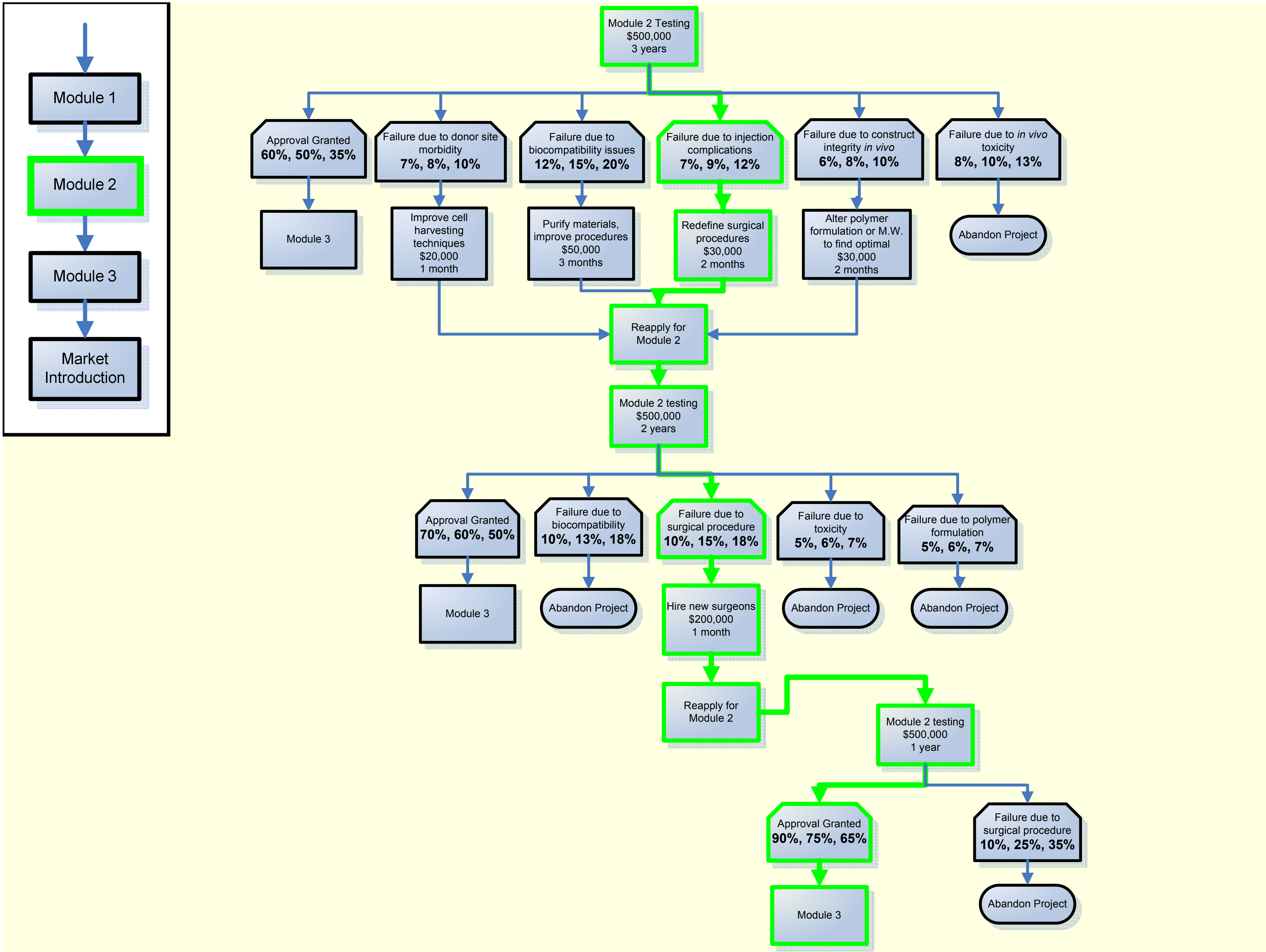
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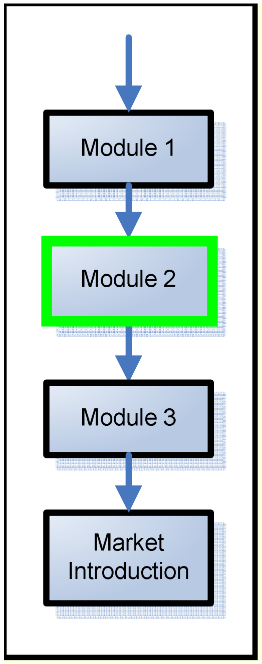
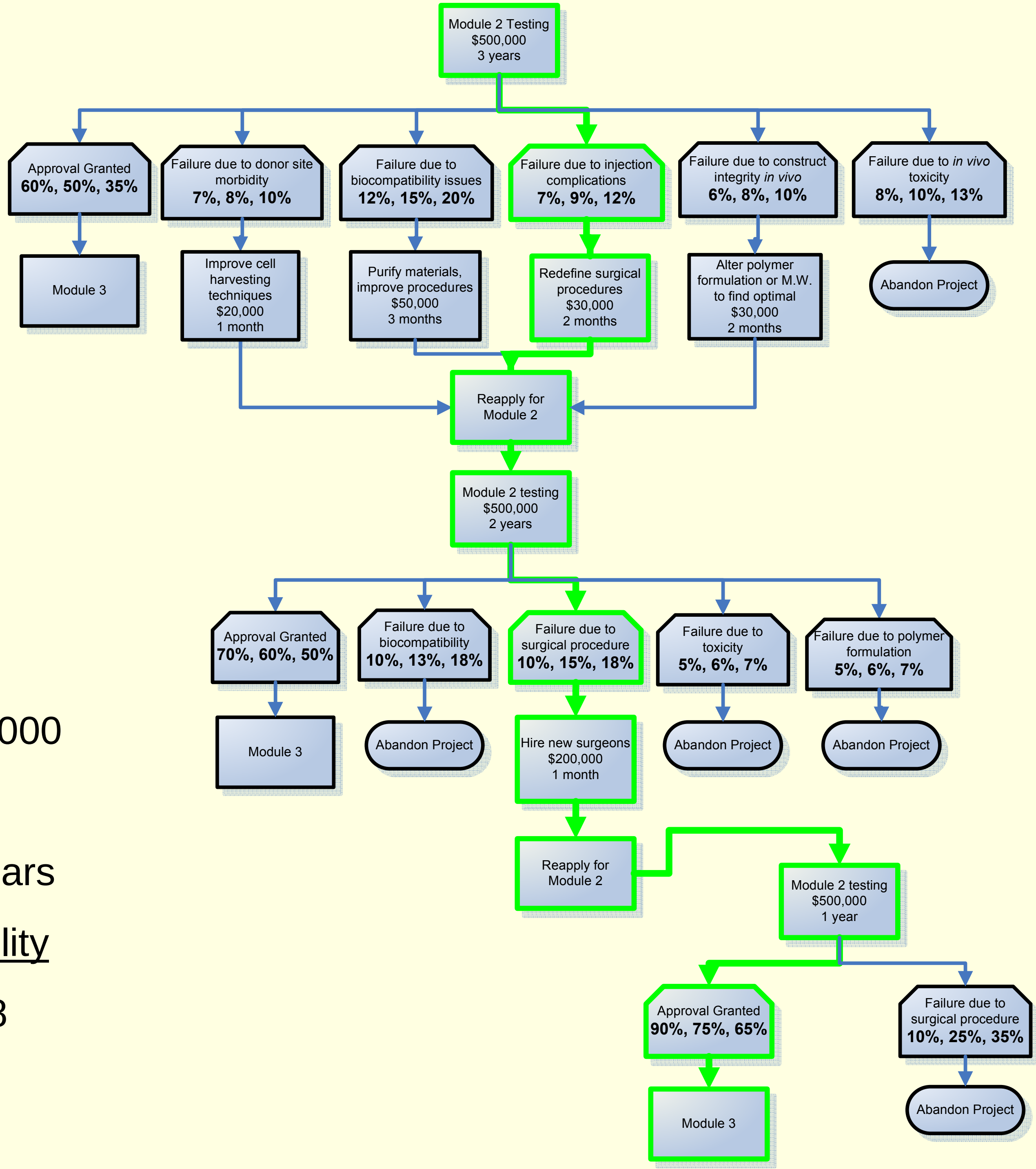




<u>Cost</u>

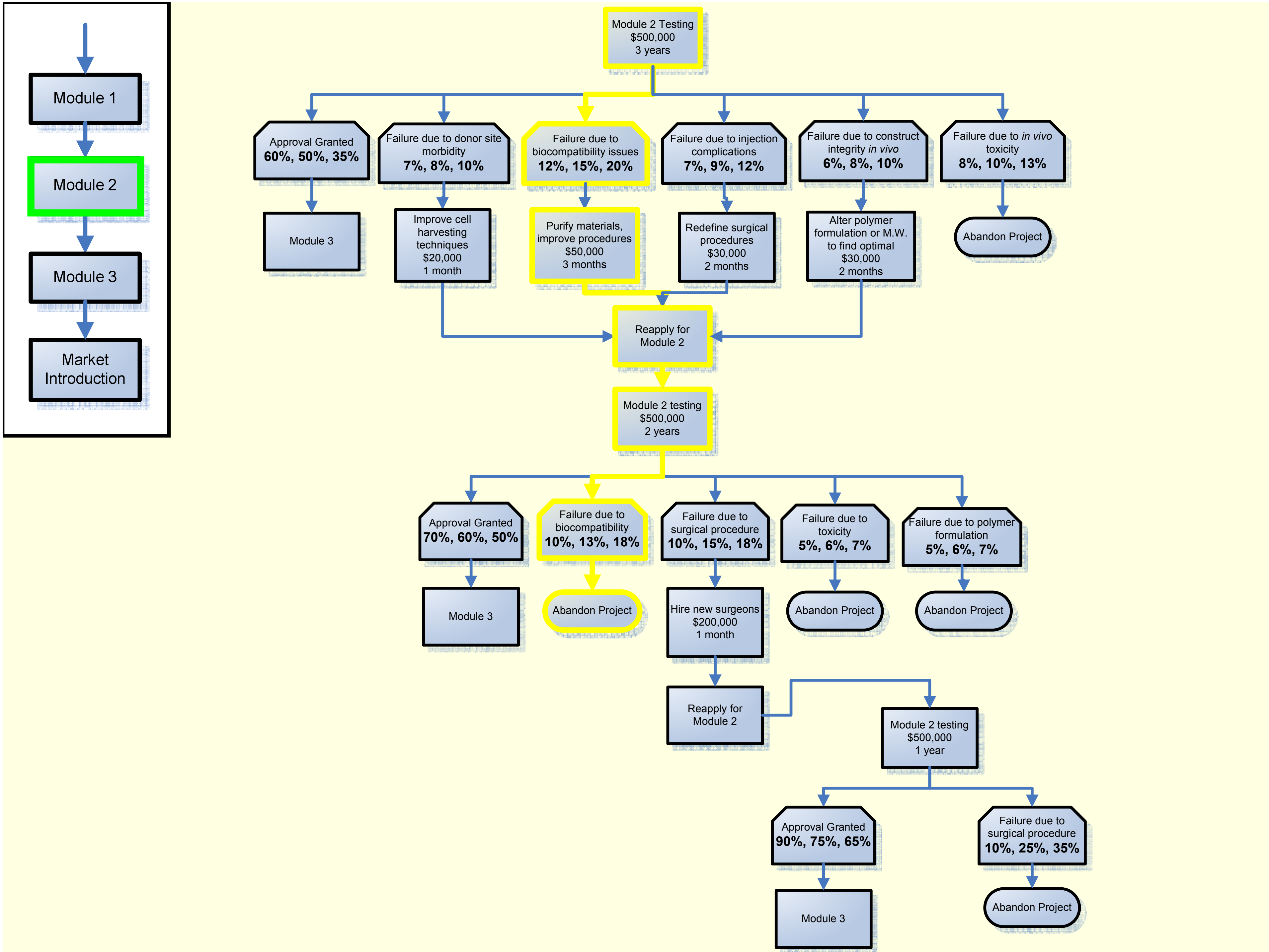
$2,660,000

<u>Time</u>

12.5 Years

<u>Probability</u>

0.00028



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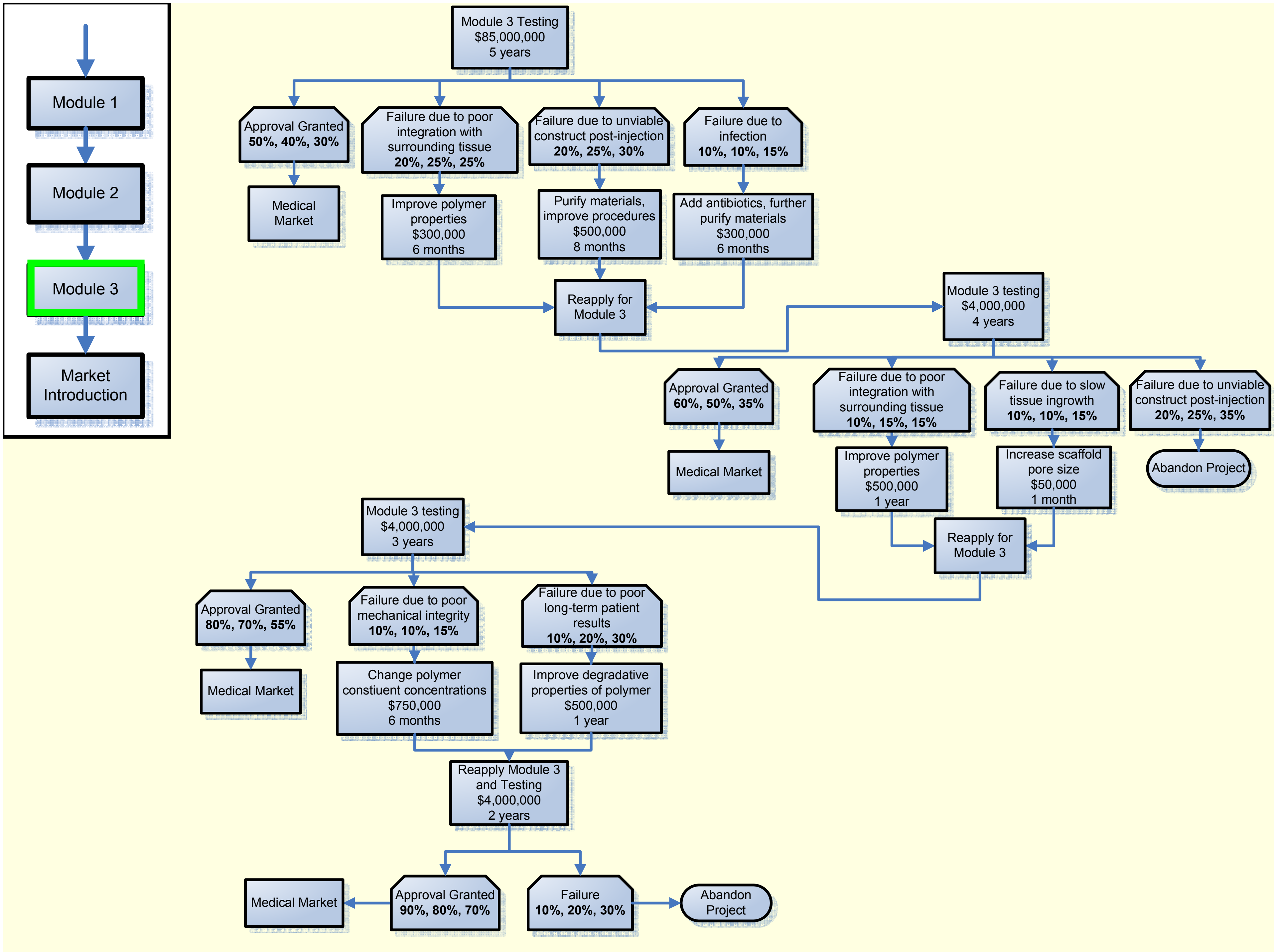
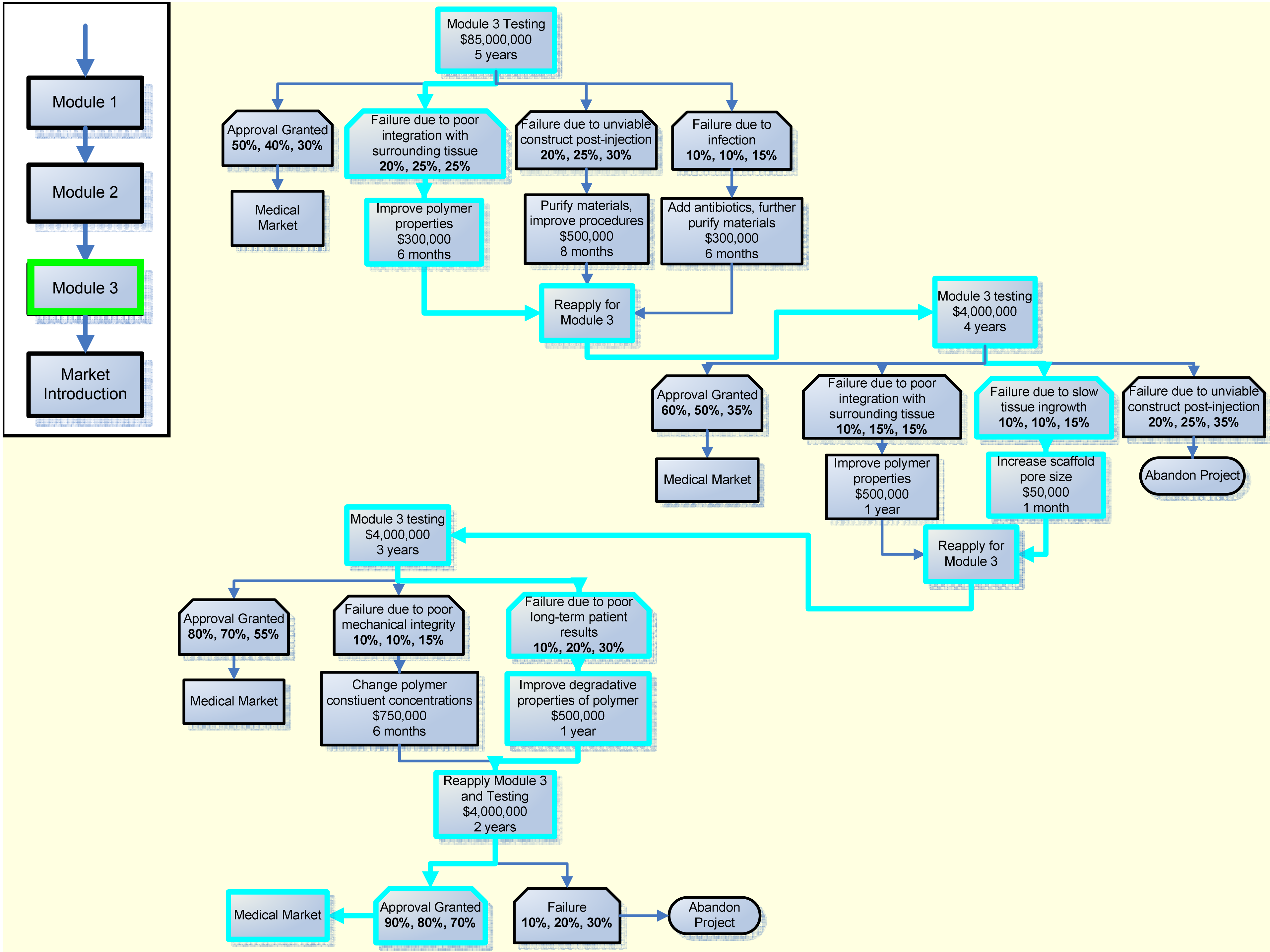
Abandon Project


Module 1
Module 2
Module 3
Market Introduction
Module 3 Testing $85,000,000 5 years
Approval Granted 50%, 40%, 30%
Medical Market
Failure due to poor integration with surrounding tissue 20%, 25%, 25%
Improve polymer properties $300,000 6 months
Failure due to unviable construct post-injection 20%, 25%, 30%
Purify materials, improve procedures $500,000 8 months
Failure due to infection 10%, 10%, 15%
Add antibiotics, further purify materials $300,000 6 months
Reapply for Module 3
Module 3 testing $4,000,000 4 years
Approval Granted 60%, 50%, 35%
Medical Market
Failure due to poor integration with surrounding tissue 10%, 15%, 15%
Improve polymer properties $500,000 1 year
Failure due to slow tissue ingrowth 10%, 10%, 15%
Increase scaffold pore size $50,000 1 month
Failure due to unviable construct post-injection 20%, 25%, 35%
Abandon Project
Reapply for Module 3
Module 3 testing $4,000,000 3 years
Approval Granted 80%, 70%, 55%
Medical Market
Failure due to poor mechanical integrity 10%, 10%, 15%
Change polymer constiuent concentrations $750,000 6 months
Failure due to poor long-term patient results 10%, 20%, 30%
Improve degradative properties of polymer $500,000 1 year
Reapply Module 3 and Testing $4,000,000 2 years
Medical Market
Approval Granted 90%, 80%, 70%
Failure 10%, 20%, 30%
Abandon Project



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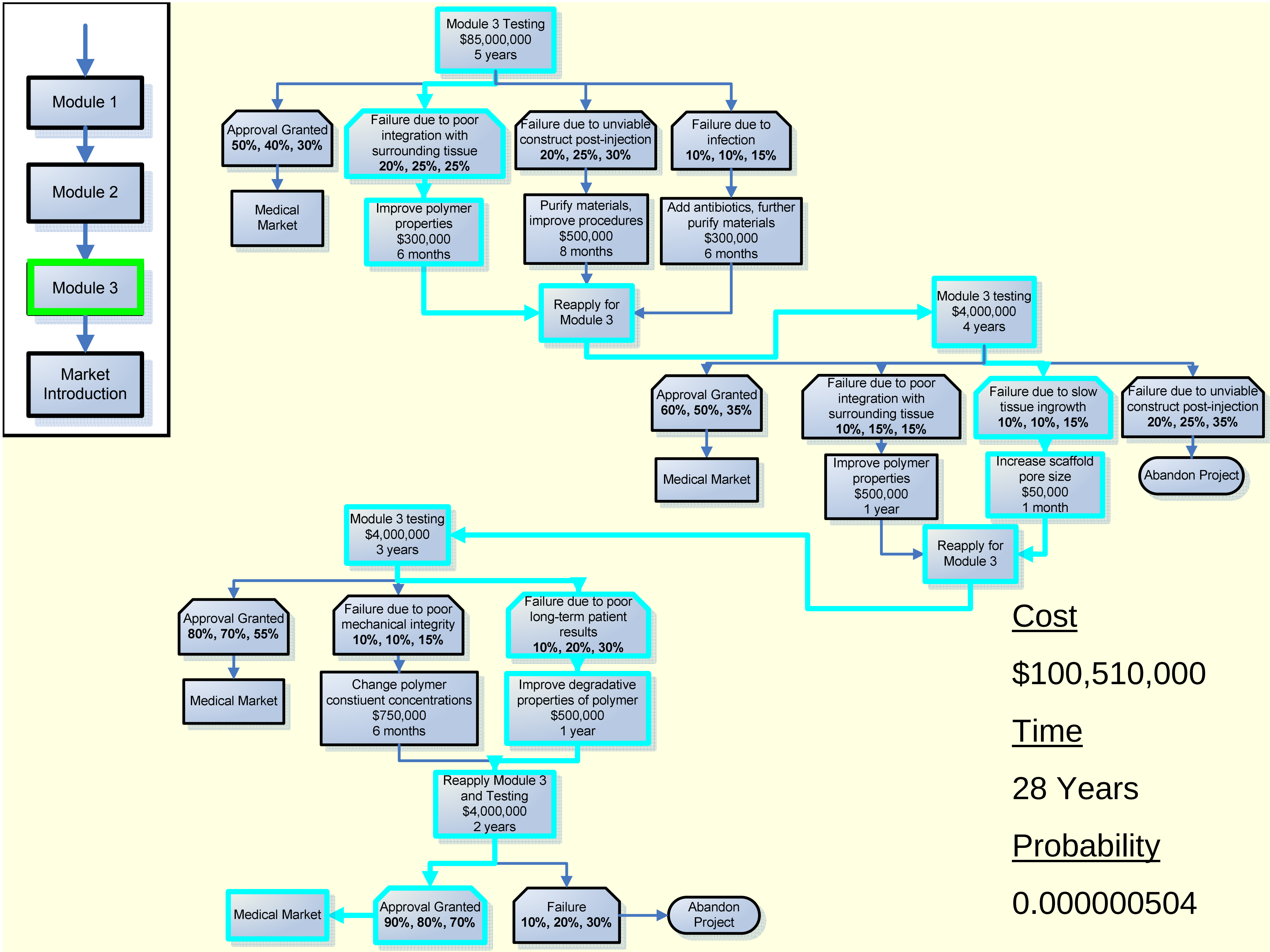


<u>Cost</u>

$100,510,000

<u>Time</u>

28 Years

<u>Probability</u>

0.000000504

Modeling Pathways

- Models can quickly become complicated
- 5,291 total pathways through FDA
  - 2,970 pathways lead to success
  - 2,321 pathways lead to failure
- First stage decisions shape FDA model
- Probabilities, time, and cost are estimated based on all available knowledge.
  - Modeling technical details increases accuracy of the FDA model.

Risk Assessment

- The probability, time until completion, and net present cost for each pathway was calculated
- Scenarios varying by the number of workers and the number of experiments were created
  - 2, 5, or 10 workers
  - 45, 60, or 70 experiments
- Net present worth of the product was calculated to evaluate the possible profit
  - Price and demand must be considered

Pricing

- To know the expected value of each pathway, the profit for each operating year must be estimated.

$$Profit_n = pd_n - IC_n d_n - FC_n$$

IC = Surgery and material cost per implant, **FC** = Fixed annual operating costs

- The price and demand are classically related by a simple expression

$$pd = Constant$$

Pricing

- How do we choose a price?

Less than competitor:	**More than competitor:**
Get the majority of the market	Get the smaller market share
Price: $15,000	Price: $35,000
Demand: ~15,000	Demand: ~7,000
Profit: ~$70,000,000	Profit: ~$170,000,000

- We will need a more detailed model to find the optimum price

Pricing

- A more detailed pricing model involves maximizing consumer utility (happiness)
- With only one competitor, the utility (U) is:

$$U = d_1^{\alpha} + d_2^{\beta}$$

α = f (knowledge)

β = f (happiness)

- This is maximized subject to two constraints:

$$p_1 d_1 + p_2 d_2 \leq Y$$

$$d_1 + d_2 \leq D$$

Y = Total Consumer Budget

D = Total Demand

Pricing

- This gives two possible equations relating demand and price:

Budget Controlled Solution

$$d_1 = \frac{\alpha}{\beta}\frac{p_2}{p_1}\left(\frac{Y - p_1 d_1}{p_2}\right)^{1-\beta} d_1^{\alpha}$$

Demand Controlled Solution

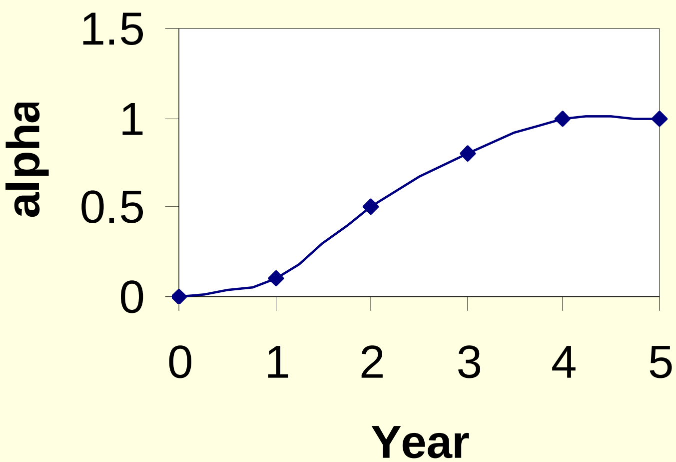
$$d_1 = \frac{\alpha}{\beta}\left(D - d_1\right)^{1-\beta} d_1^{\alpha}$$

- These are both solved for d_1; the lower solution satisfies both constraints.

Pricing

- Estimating α and β:

Knowledge increases gradually until it becomes perfect (α = 1)



β is estimated by assuming happiness values and weights for various attributes

$$\beta = \frac{H_2}{H_1} = \frac{\sum w_i y_{2,i}}{\sum w_i y_{1,i}} = 0.8$$

Description	*Weight*	y_1	y_2
Long-term outcome	0.70	1	0.8
Invasiveness	0.15	0.8	0.4
Recovery Time	0.15	0.75	0.65

Pricing

- Estimating Y and D
  - Values are assumed from knowledge of the competitor's current market and statistics on the number of people with this kind of knee problem.

Y = $250,000,000 / year

D = 15,000 Implants / year

Pricing

- The demand and the profitability were evaluated for a range of prices.
- When α = 1, the maximum profitability was found at:

p_1 = $95,000

d_1 = 2573 Implants / year

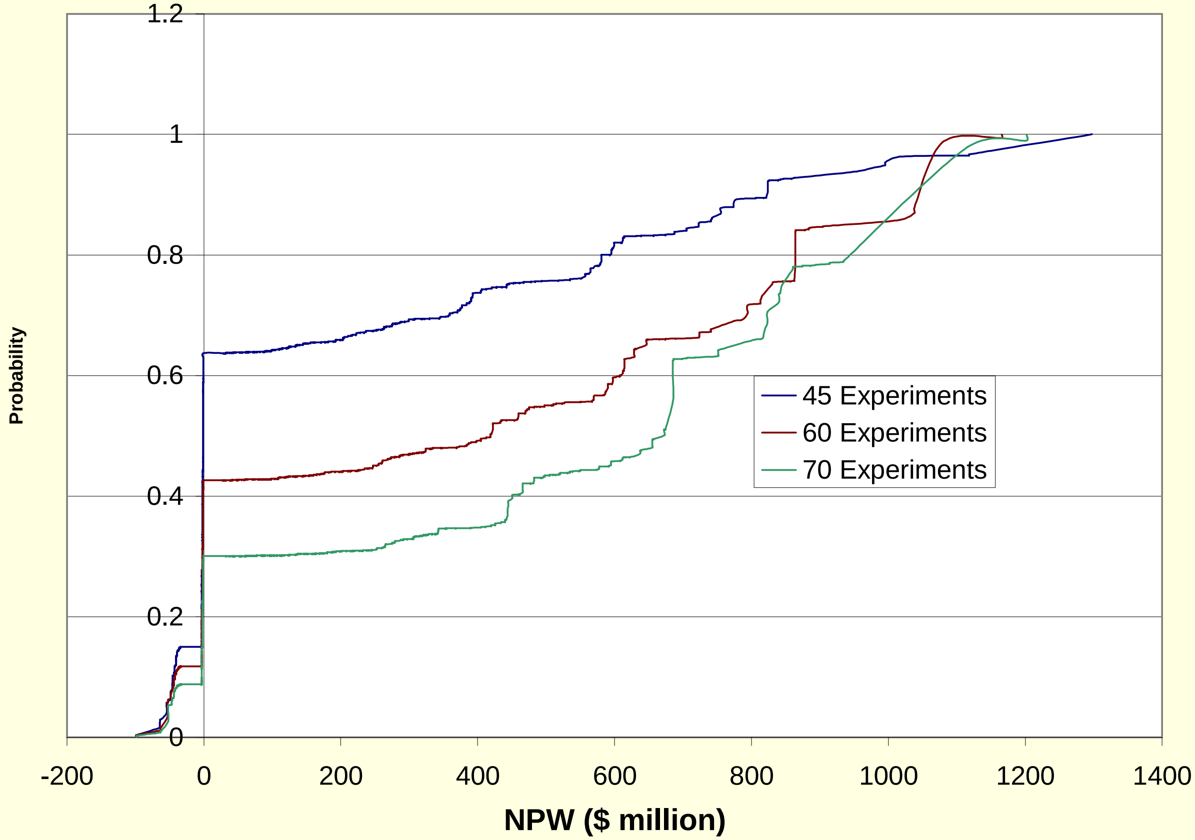
Profit = $217,000,000 / year

- This price was used to find profitability during the first five years

Year 1	Year 2	Year 3	Year 4	Year 5
$0	-$500,000	$600,000	$217,000,000	$217,000,000

Risk Curve

- These profits during operation give these risk curves for the NPW forty years from now



Pricing Model Deviations

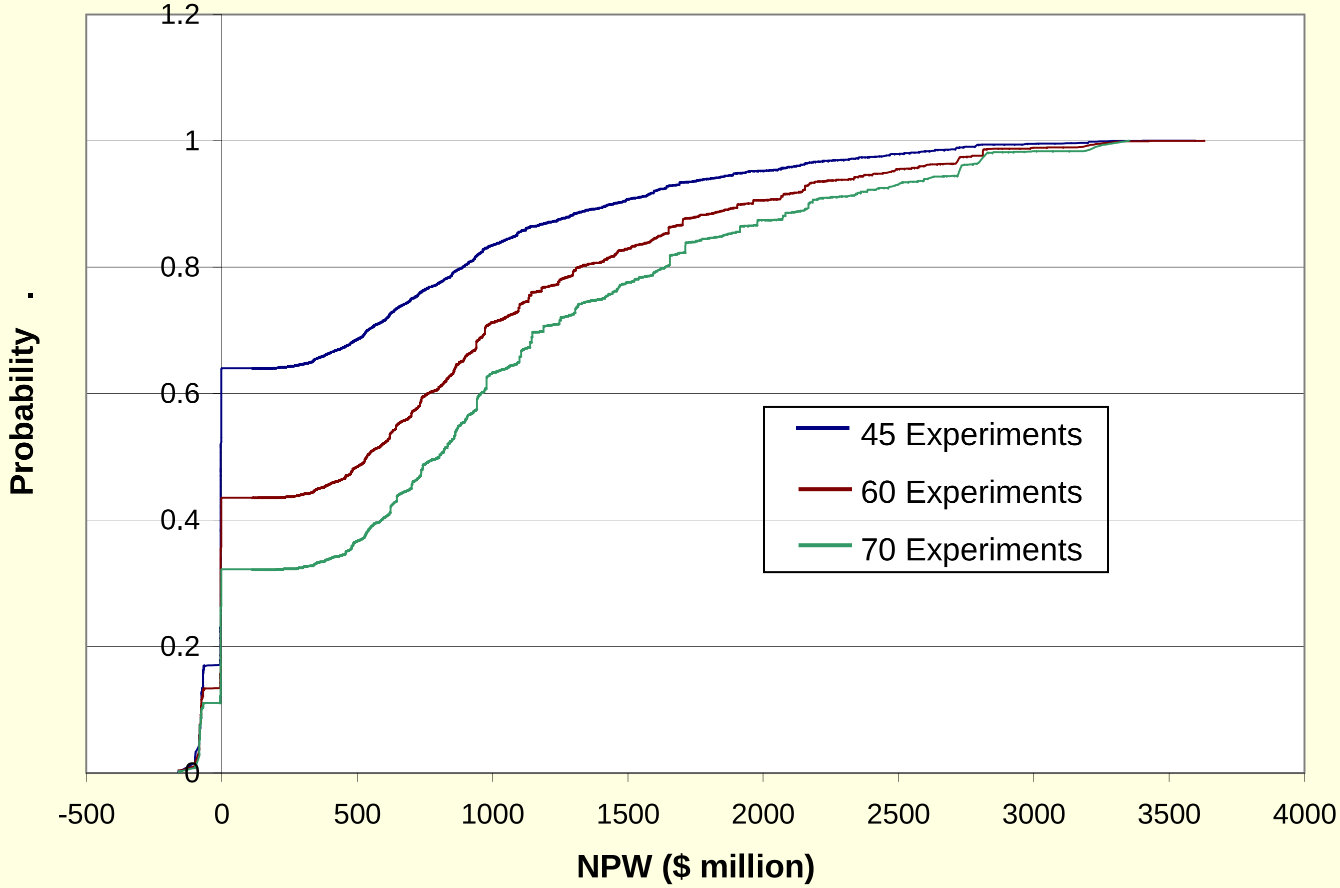
- The values used for α, β, Y, and D are variable.
- To make this evaluation more rigorous, several values of each are used with their associated probabilities.

α (years to reach 1)	5 (50%)	4 (33%)	3 (17%)
β	0.5 (25%)	0.8 (50%)	0.999 (25%)
Y	$150,000,000 (33%)	$250,000,000 (33%)	$400,000,000 (33%)
D	10,000 (33%)	15,000 (33%)	20,000 (33%)

Profitability

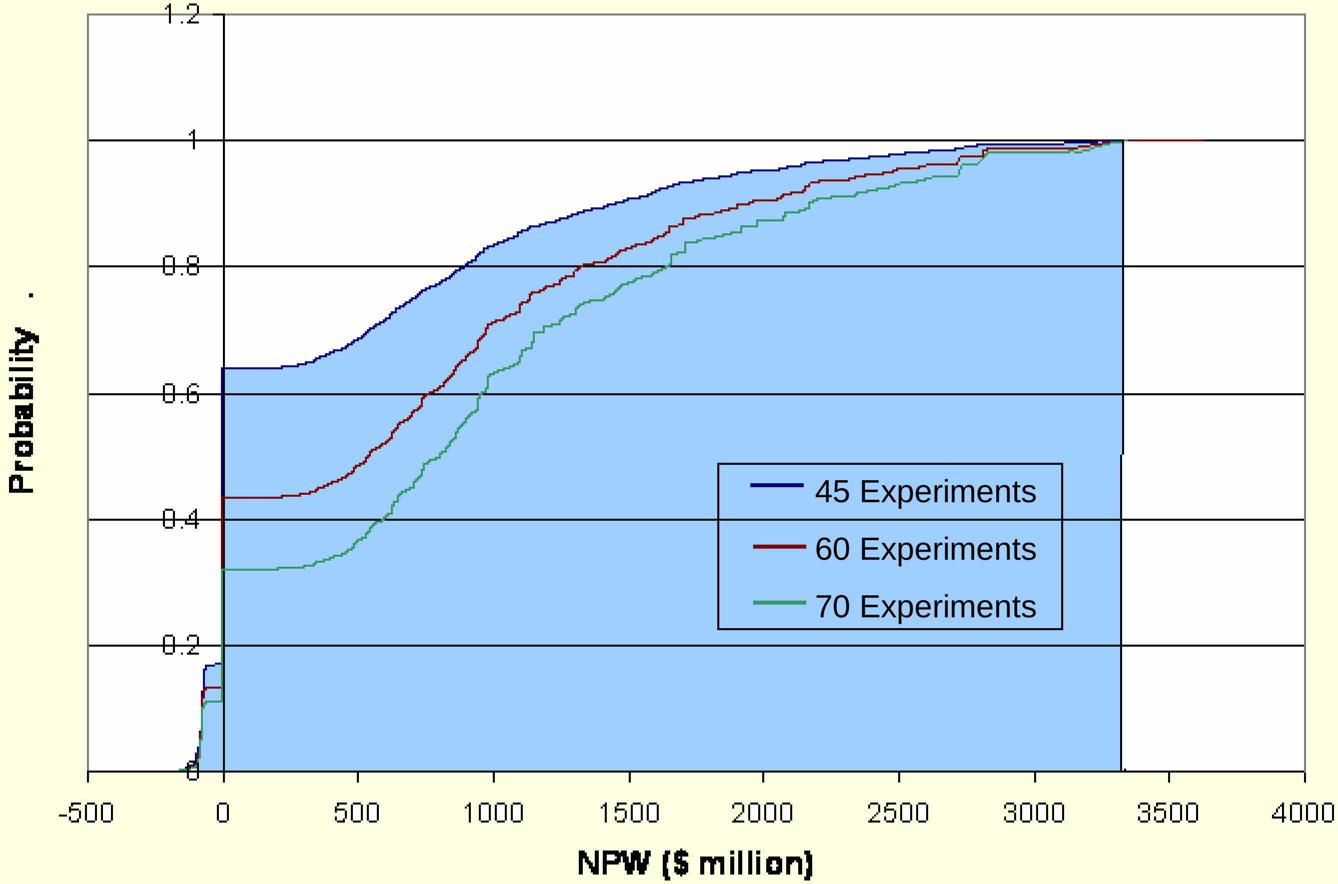
- The most profitable price for each scenario, is most strongly dependent on β.
- Changing D values have no effect on profitability; Budget constraint dominates at high prices.
- When products are almost equal (β = 1), most profitable price is competitor’s price.
- For low values of β, the most profitable price is surprisingly large - as much as $590,000!
- We may want to charge lower prices to capture a larger segment of the market.

2 Workers



1.2
1
0.8
0.6
0.4
0.2
0
Probability
-500
0
500
1000
1500
2000
2500
3000
3500
4000
NPW ($ million)
45 Experiments
60 Experiments
70 Experiments

2 Workers



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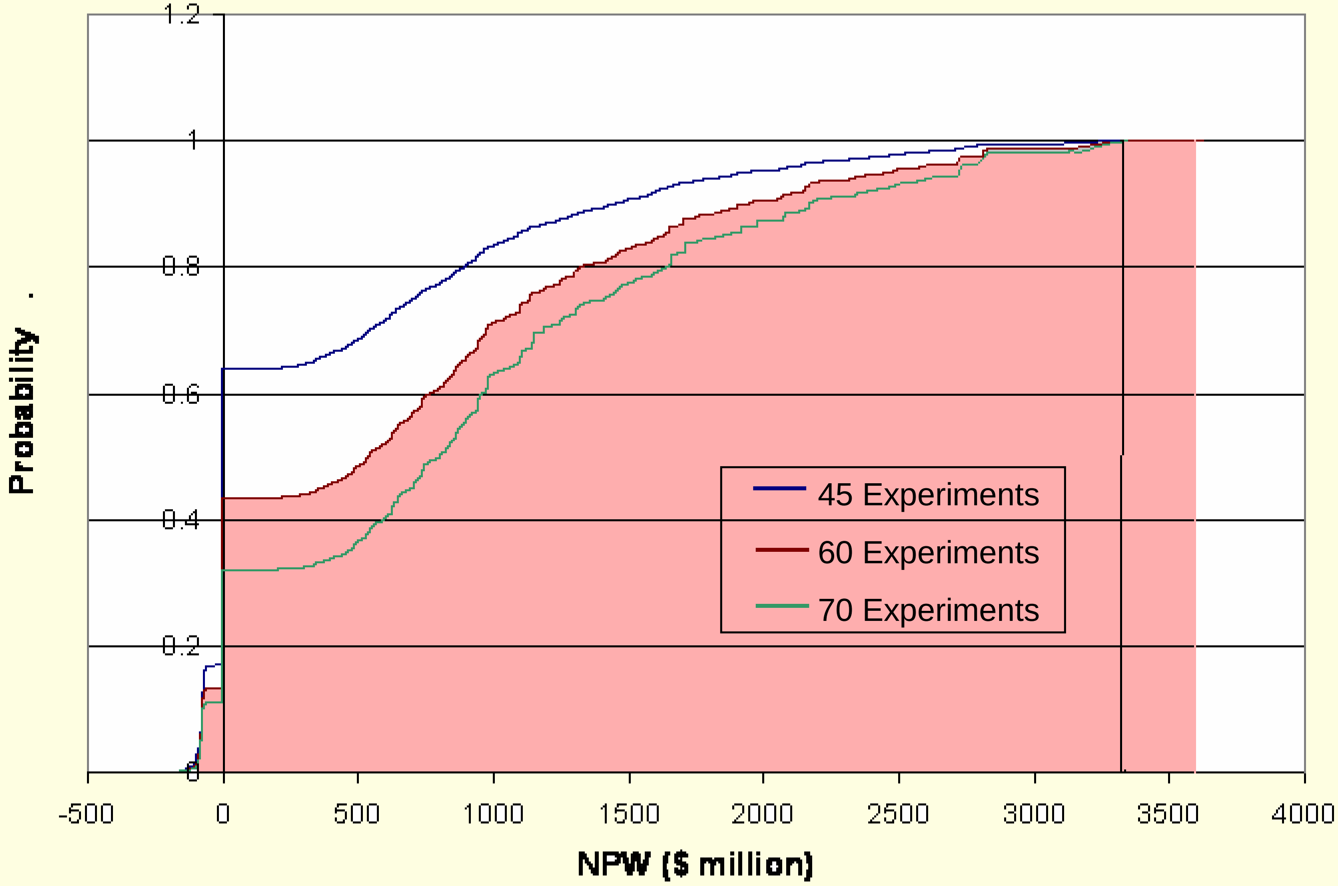

Probability
NPW ($ million)
1.2
1
0.8
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0.4
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-500
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1500
2000
2500
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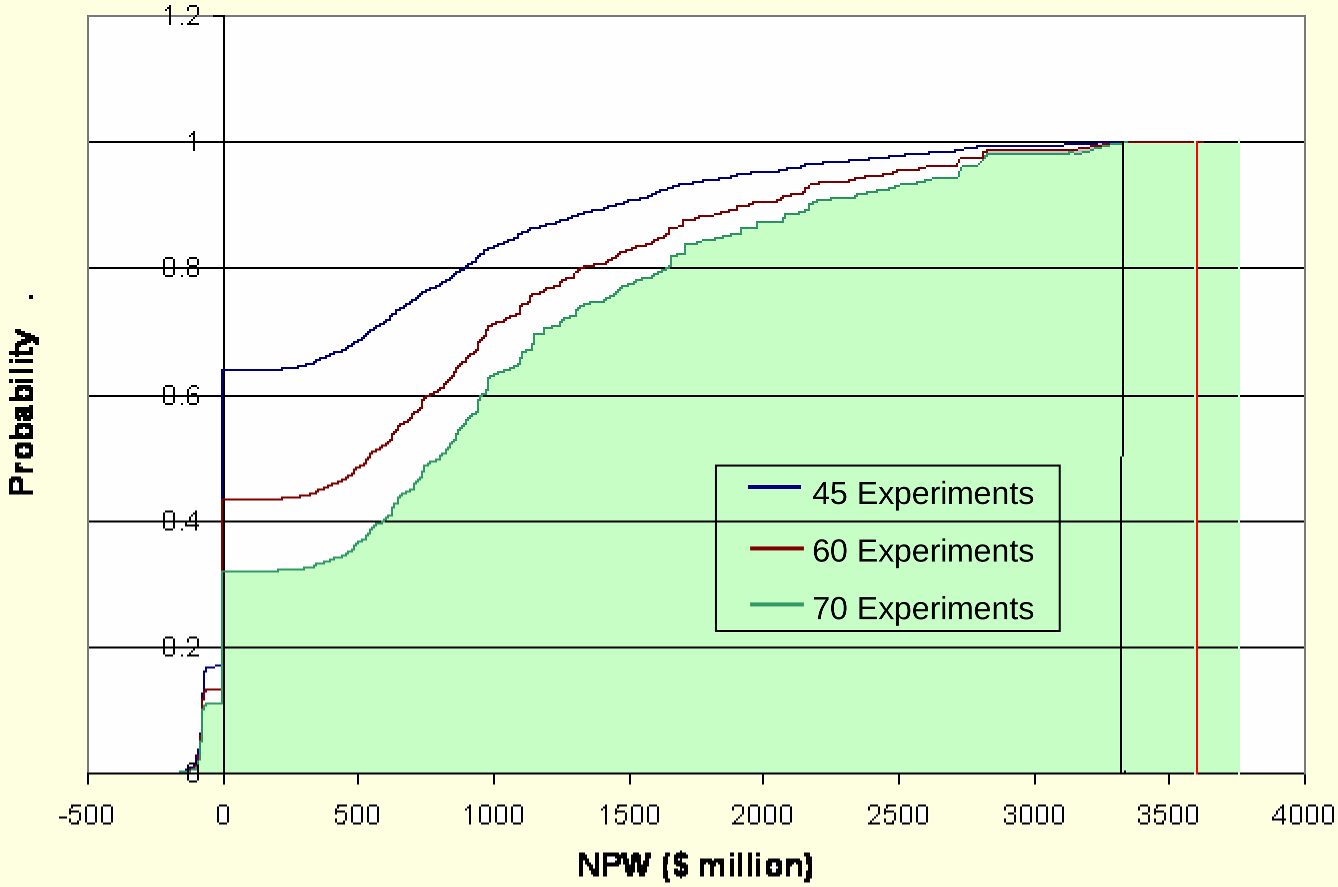
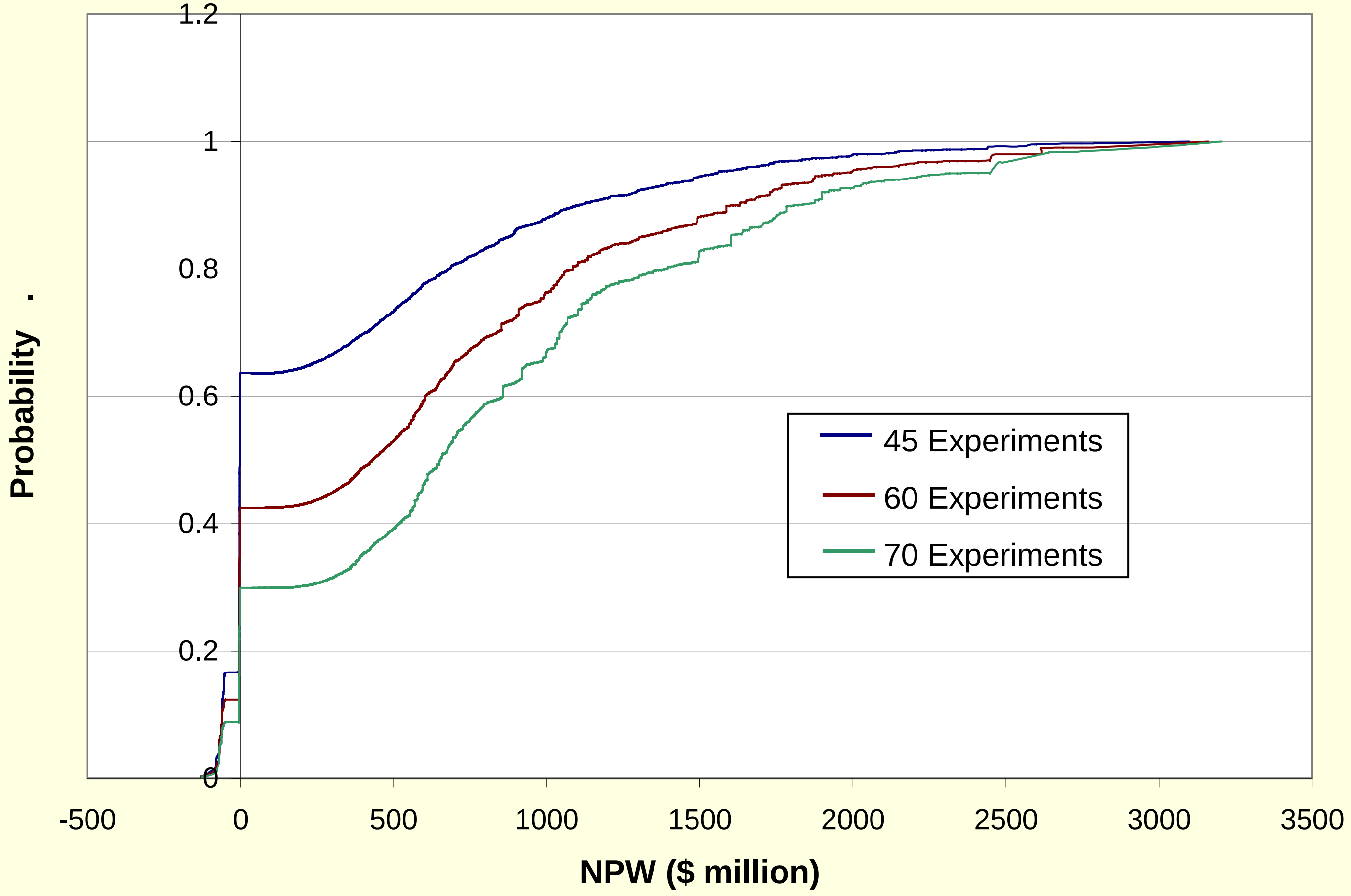
2 Workers



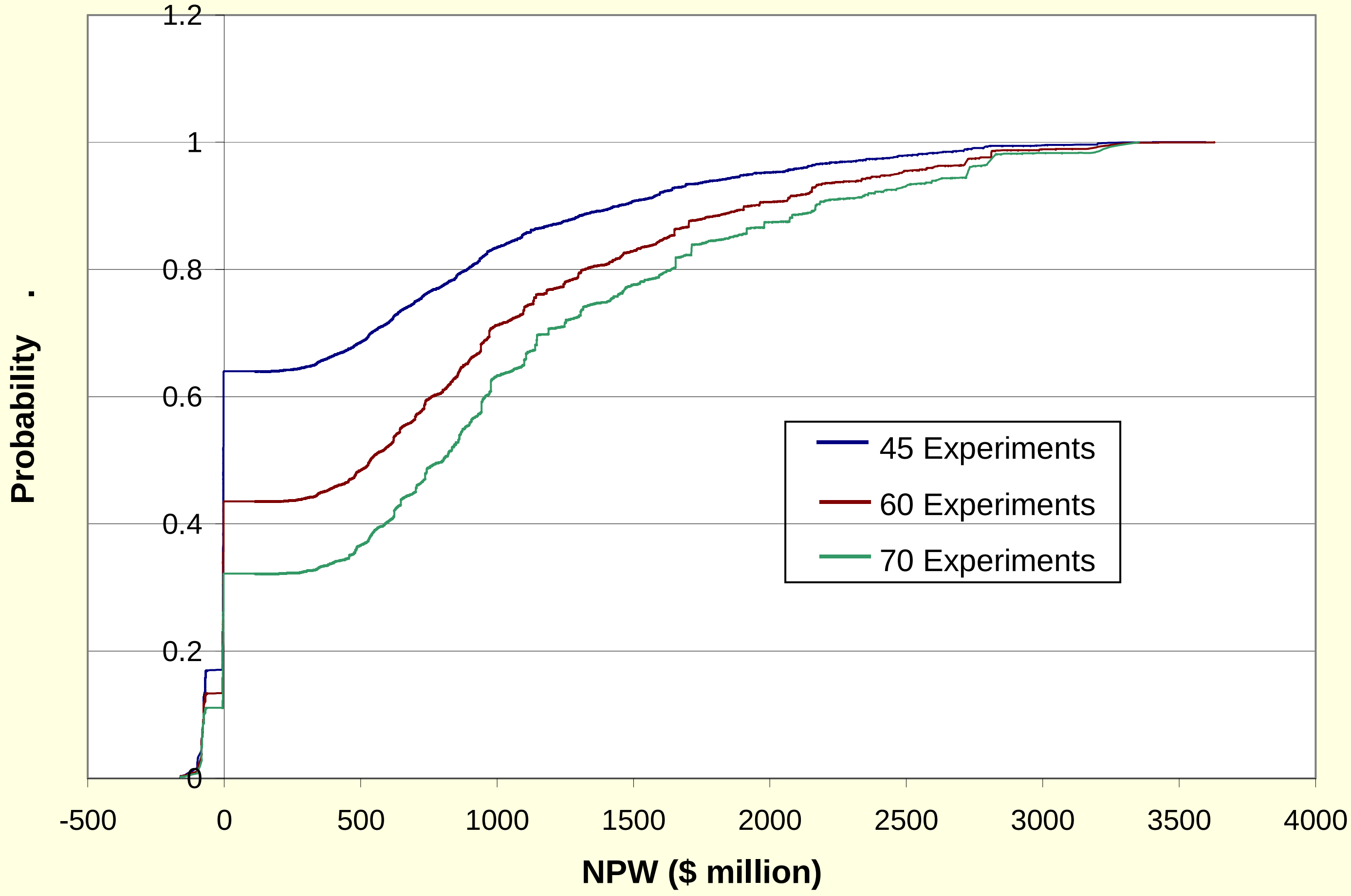
1.2
1
0.8
0.6
0.4
0.2
0
Probability
-500
0
500
1000
1500
2000
2500
3000
3500
4000
NPW ($ million)
45 Experiments
60 Experiments
70 Experiments

5 Workers



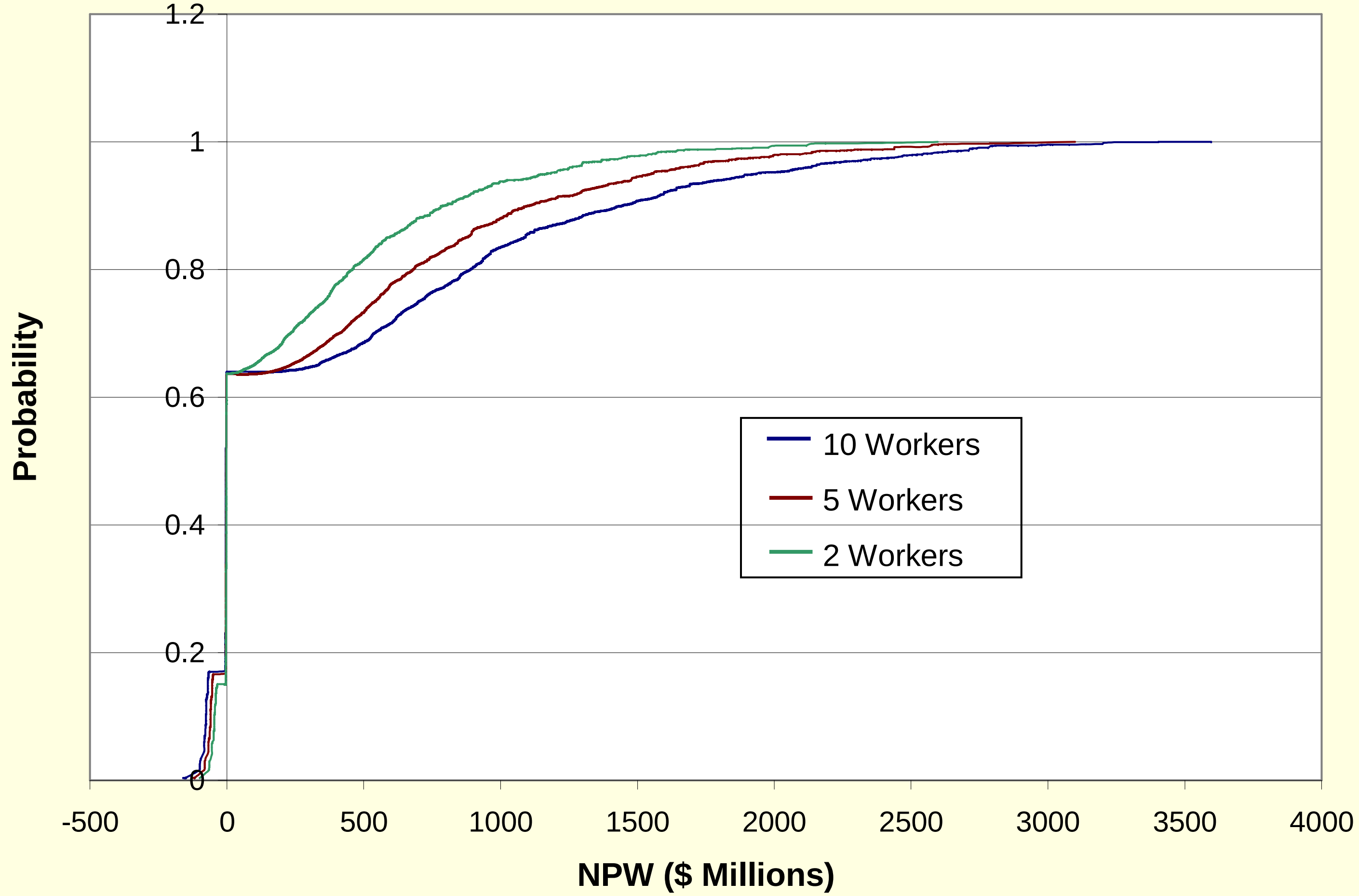
1.2
1
0.8
0.6
0.4
0.2
0
Probability
-500
0
500
1000
1500
2000
2500
3000
3500
NPW ($ million)
45 Experiments
60 Experiments
70 Experiments

10 Workers



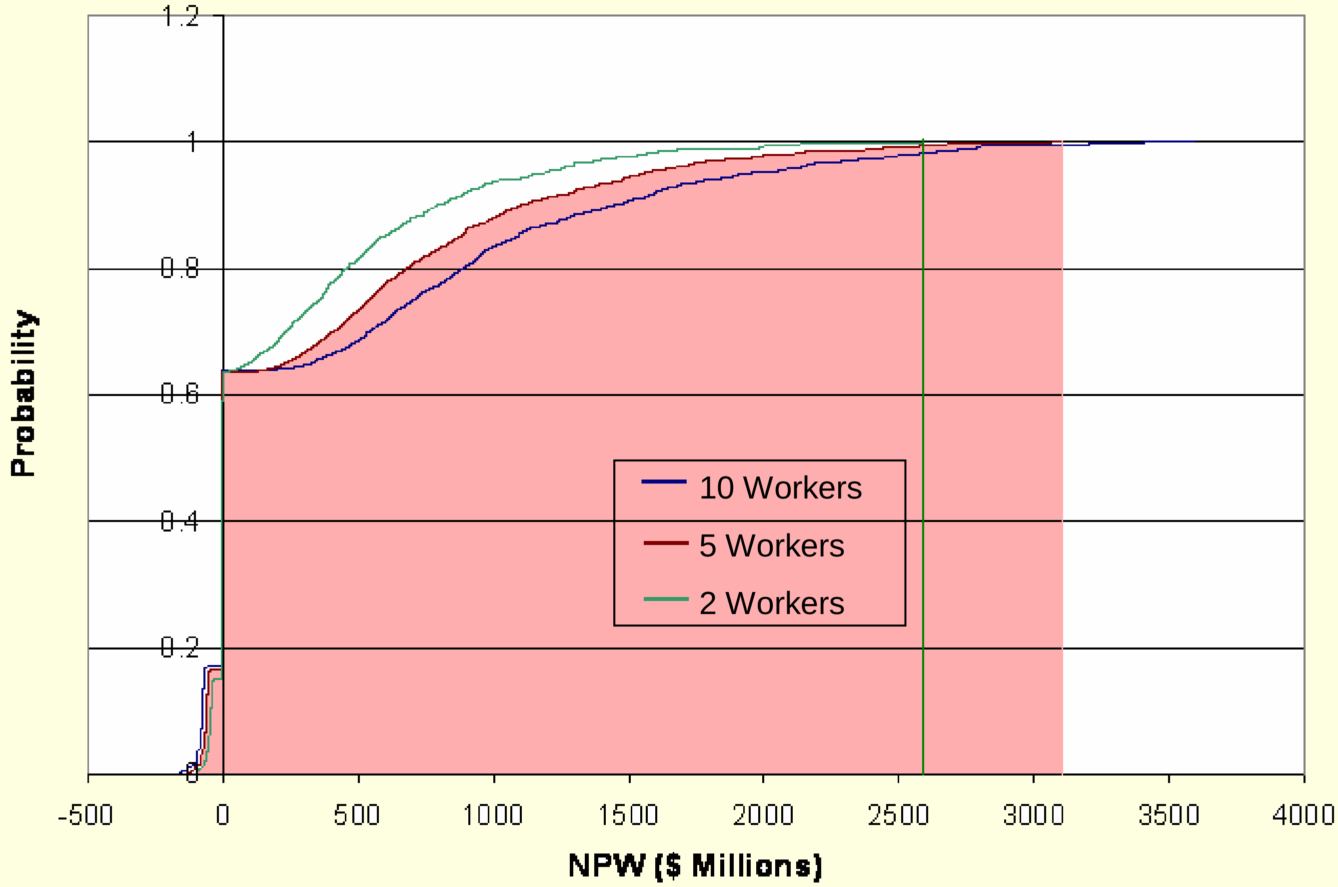
Probability
NPW ($ million)
0
0.2
0.4
0.6
0.8
1
1.2
-500
0
500
1000
1500
2000
2500
3000
3500
4000
45 Experiments
60 Experiments
70 Experiments

45 Experiments

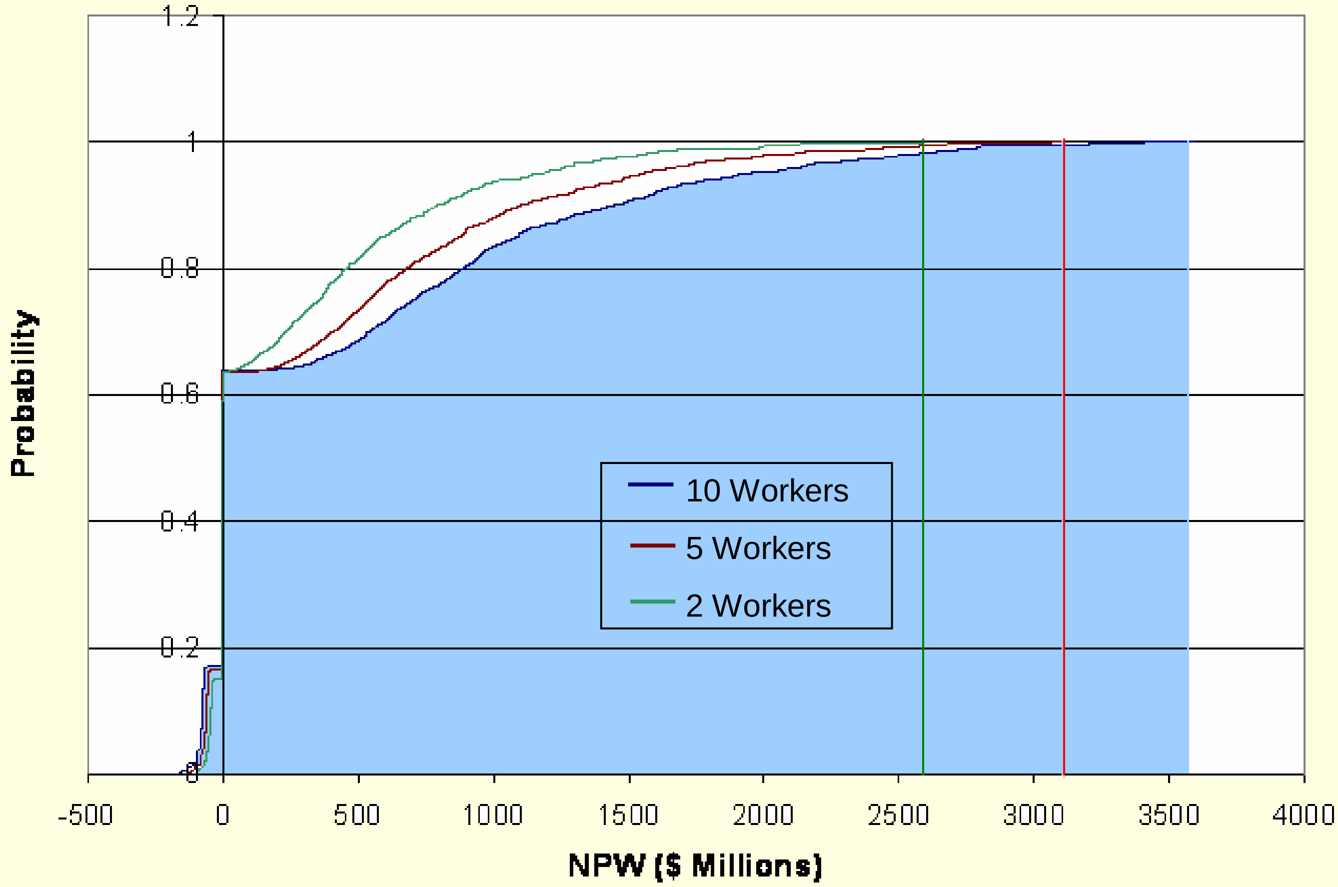


45 Experiments

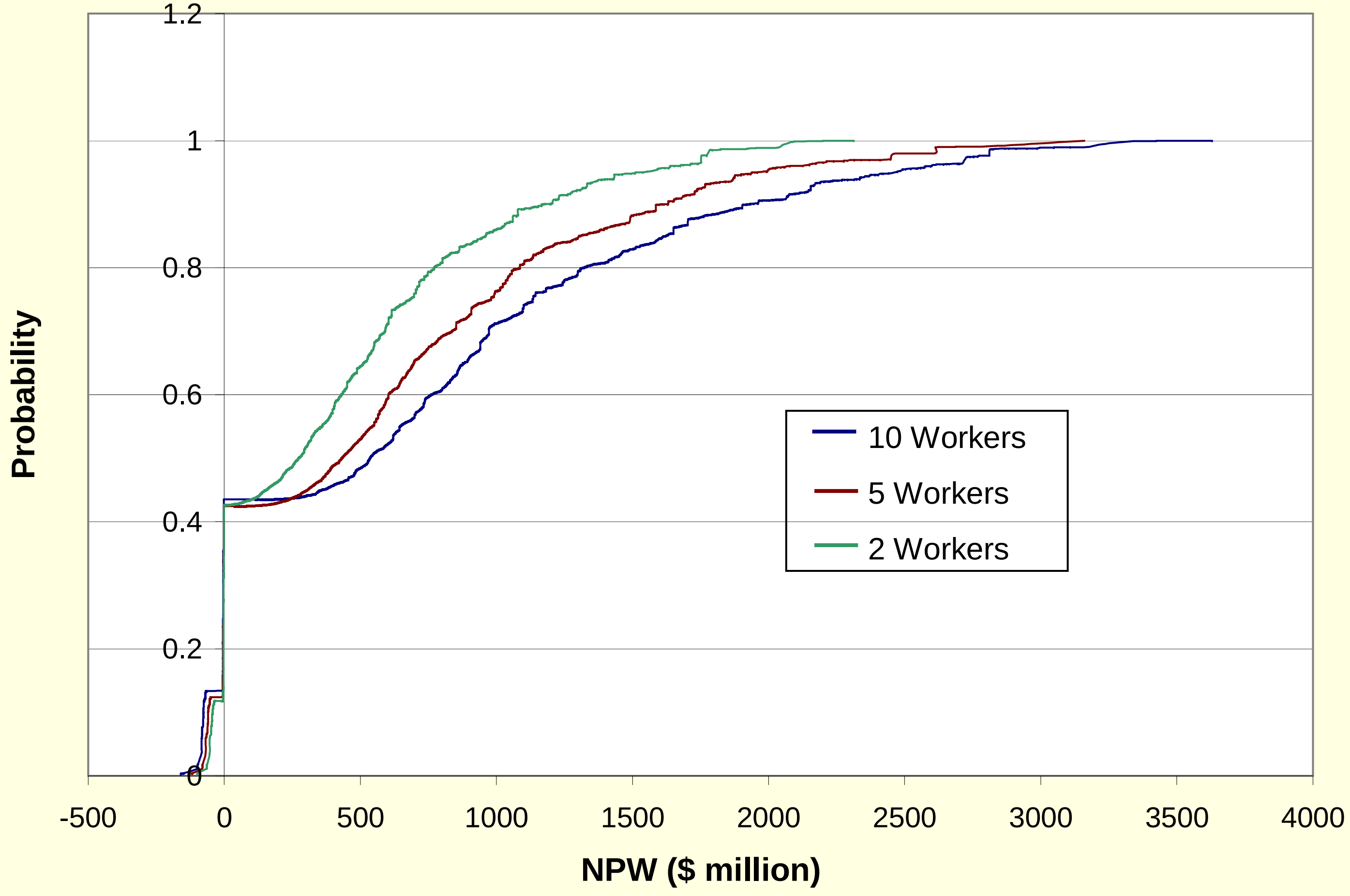
45 Experiments



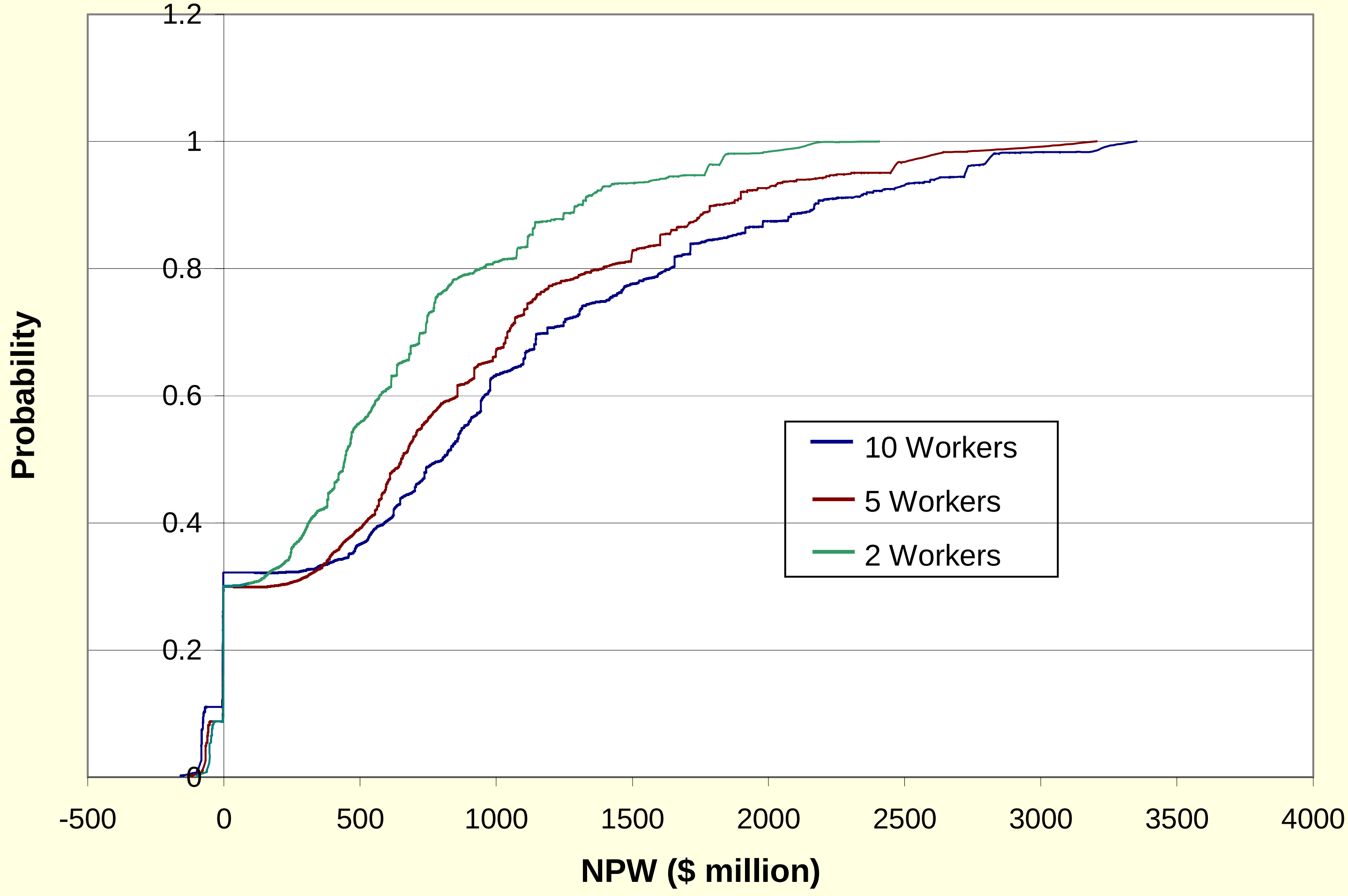
45 Experiments



60 Experiments



70 Experiments



Profitability Conclusions

- This process has the possibility of being remarkably profitable.
- The expected NPW can increase by:
  - Increasing the number of experiments
  - Increasing the number of workers
- The costs associated with these first stage decisions is minimal when compared to the possible gains.
- There are inherent limitations to how much the NPW would be expected to increase.

Conclusions

- Cartilage damage is a problem that may be solved with a tissue engineered solution
- Mathematical modeling can help to guide experimentation and give insight into a process.
- The FDA process can be modeled, with first stage decisions taken into consideration.
- Risk analysis does have some limitations, but is useful in deciding if this procedure is a worthwhile investment.