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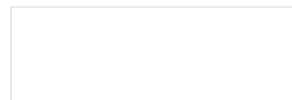
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Optimizing Development Economics

A Phase I Perspective

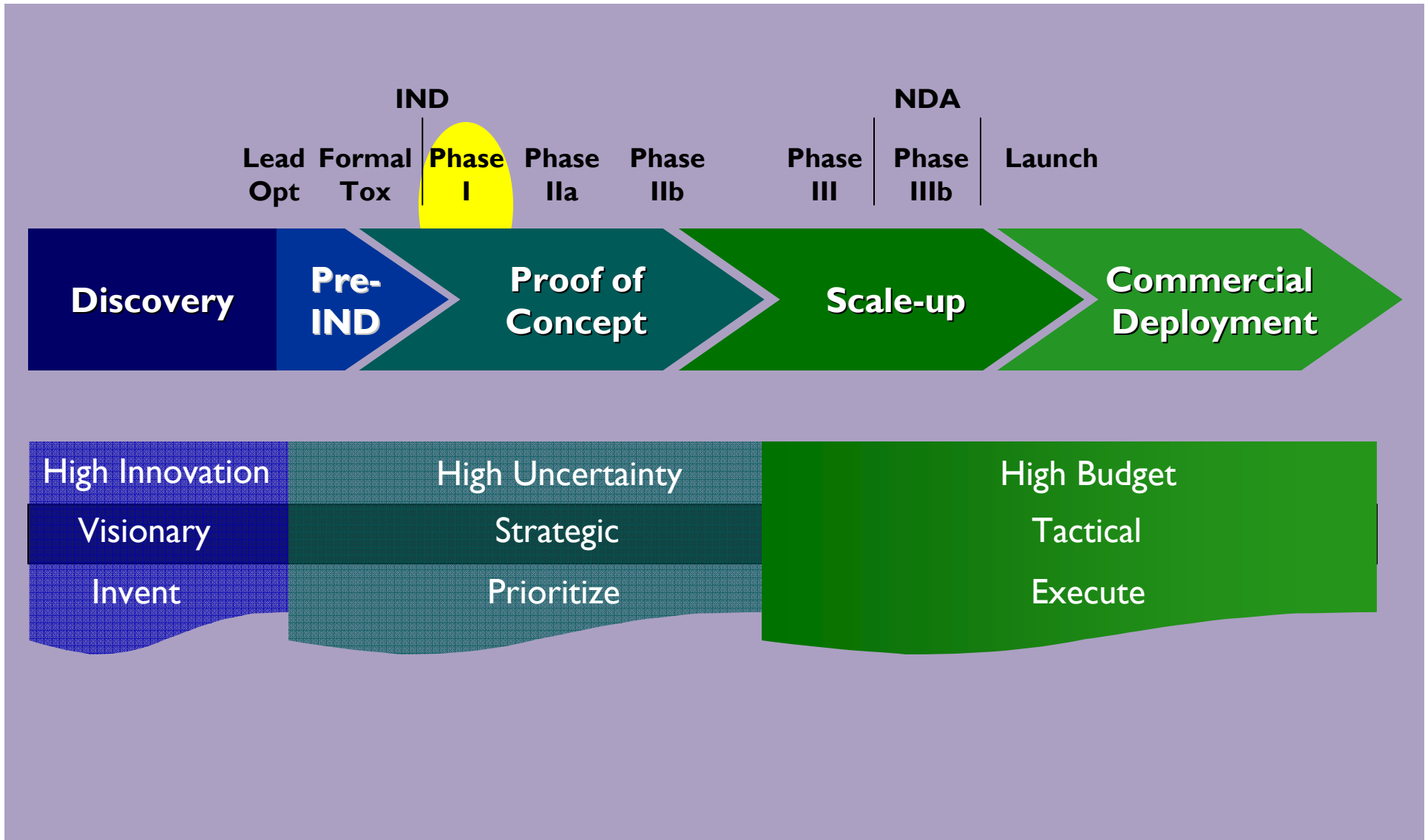
IIR 2007 Phase I Conference

October 2007
Cambridge MA



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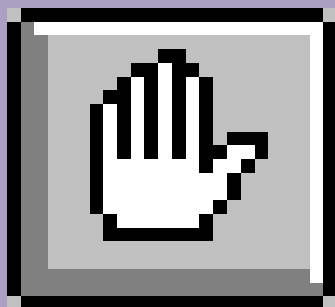
Phase I begins a drug's most strategically sensitive development period.



When entering Phase I all drug candidates look great.

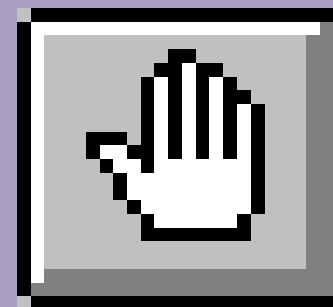
- ✓ All have completed preclinical trials and IND registration.
- ✓ Many competing compounds have already been discontinued.
- ✓ Most candidates promise large economic and human value.
- ✓ Each is endorsed by one or more proponents ...
 - ... and opposed by some detractors.
- ✓ In many cases, reputations and careers are on the line.
- ✗ Most will never become marketed drugs.
- ✗ The company does not have the resources to develop them all.

Knowing that most Phase I candidates will eventually fail creates a dilemma.



On the one hand ...

- We do not want to develop compounds destined to fail.
 - We want compounds that will eventually fail to do so quickly.
- We need to quickly and reliably anticipate compound failure.
- Discontinued compounds make resources available.



On the other hand ...

- We want to have a rich pipeline to support our valuation.
- We get milestone payments if the compound reaches phases II & III.
- Dr. Champion swears by this compound.
- Enough compound failures can kill the company.
 - # reflects company size.

What is a compound in development worth?

- We must answer three essential questions:
 - **Probability of Success:** Going forward, how likely is the compound to succeed?
 - What remains to be accomplished for the compound to succeed?
 - **Cost to Success:** What remaining resources are needed to reach success?
 - **Value Given Success:** What value would a successful compound generate?
- Then (very simplistically):

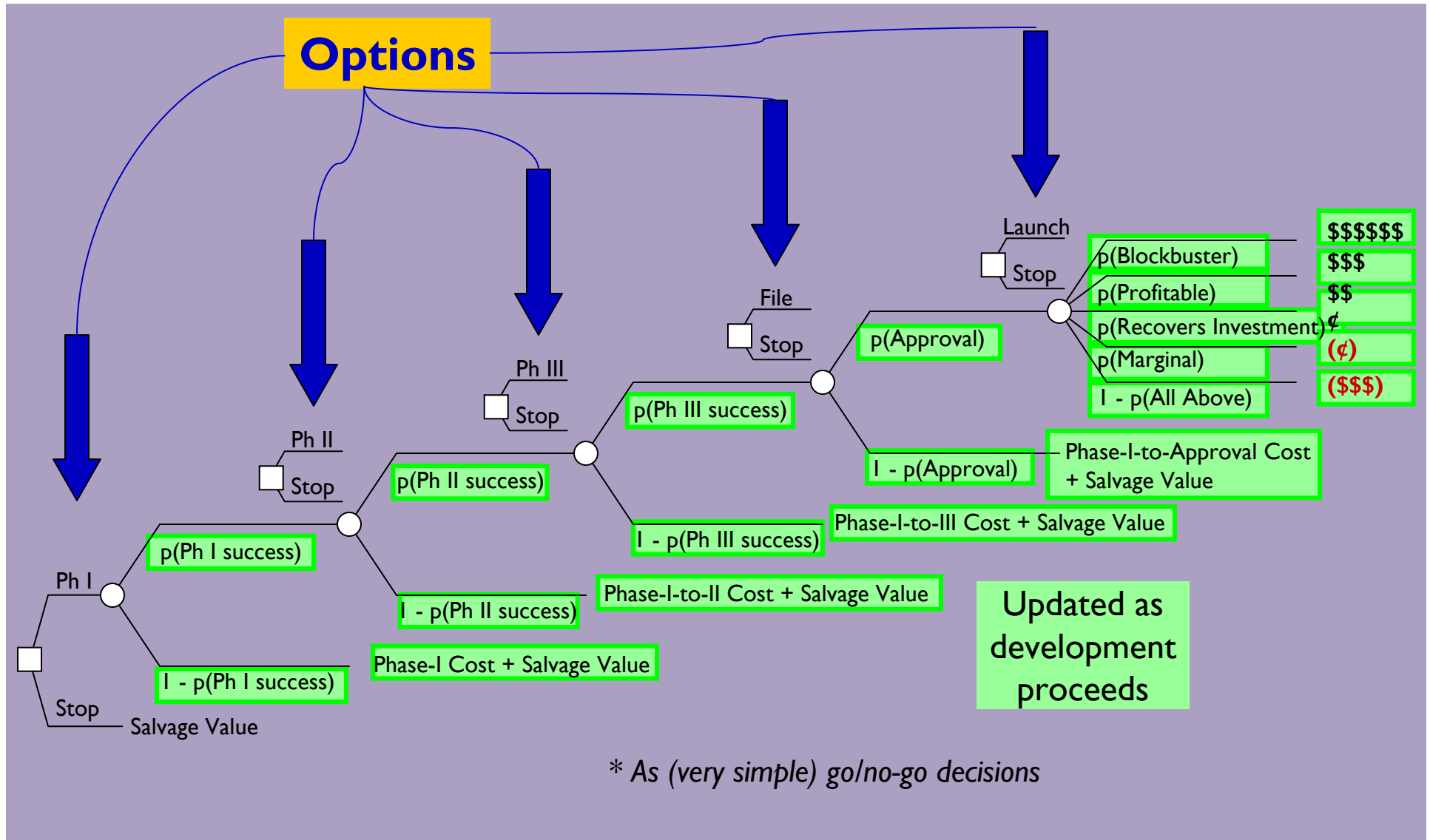
$$\text{Project Value} = \text{Probability of Success} * [\text{Value Given Success} - \text{Cost to Success}]$$

What is a compound in development worth?

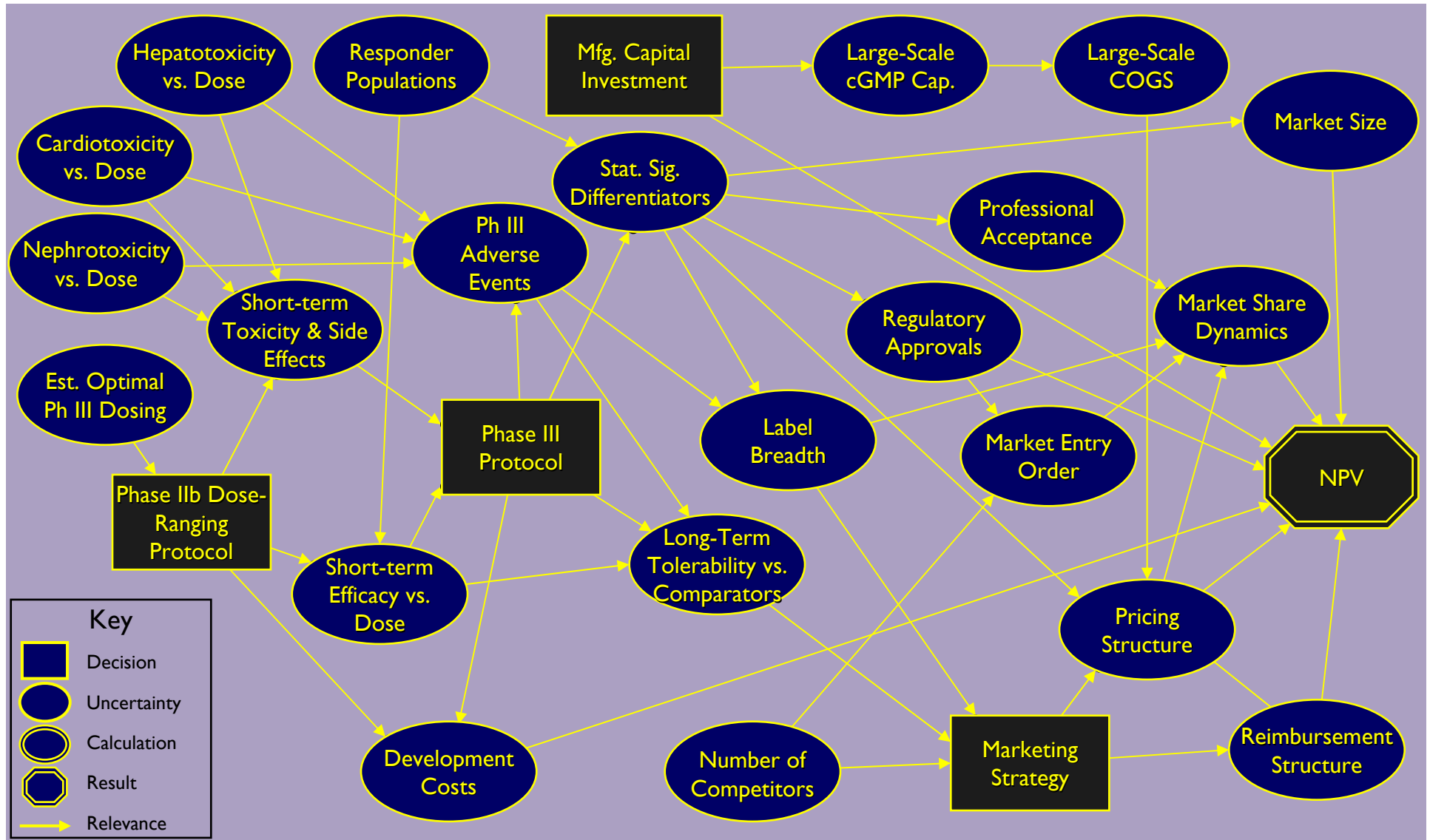
- But if:
Project Value = Probability of Success * [Value Given Success – Cost to Success]
- Then: Do the math ...
... all drug development projects would be losing bets.
i.e., they would have negative NPV.
- So why are pharmaceutical companies in business?
- Because, for one, project cost is not committed all at once.

When viewed as a sequence of **options**, many – but not all – pharmaceutical projects are good investments. (Some are exceptional.)

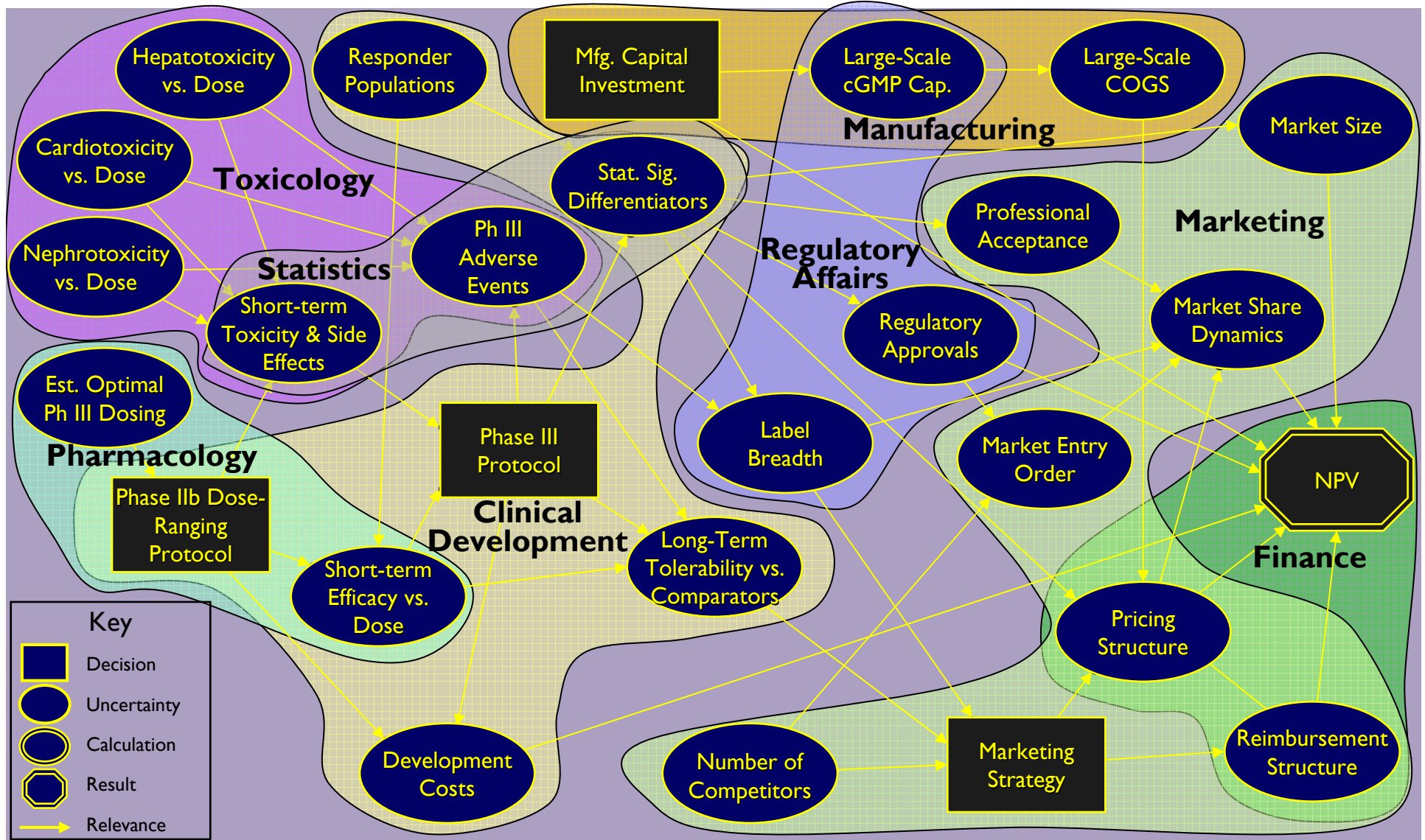
As a sequence of options, a drug-development project looks like a decision tree*.



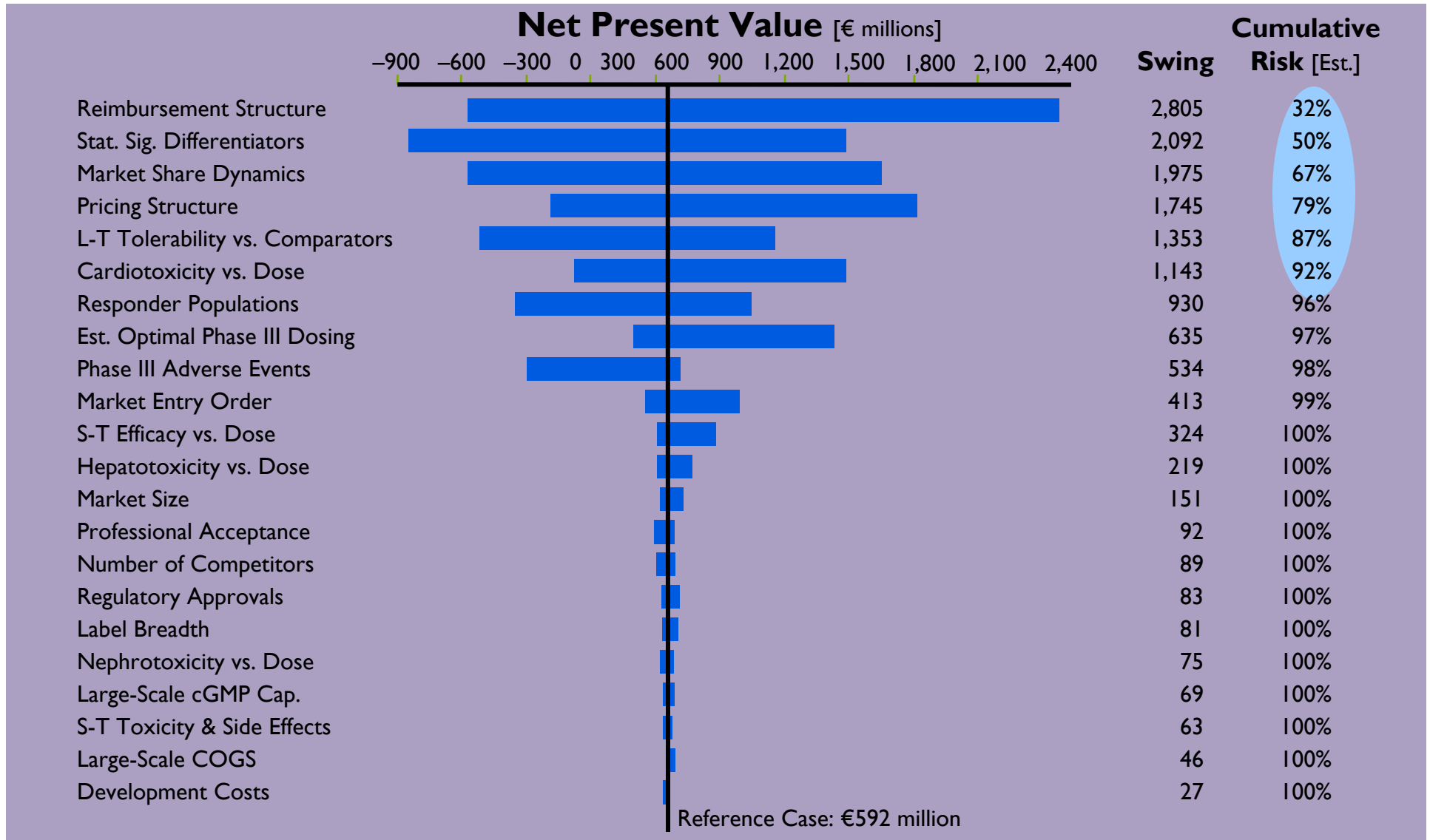
A closer look reveals that the many factors that drive a pharmaceutical decision are highly interrelated.



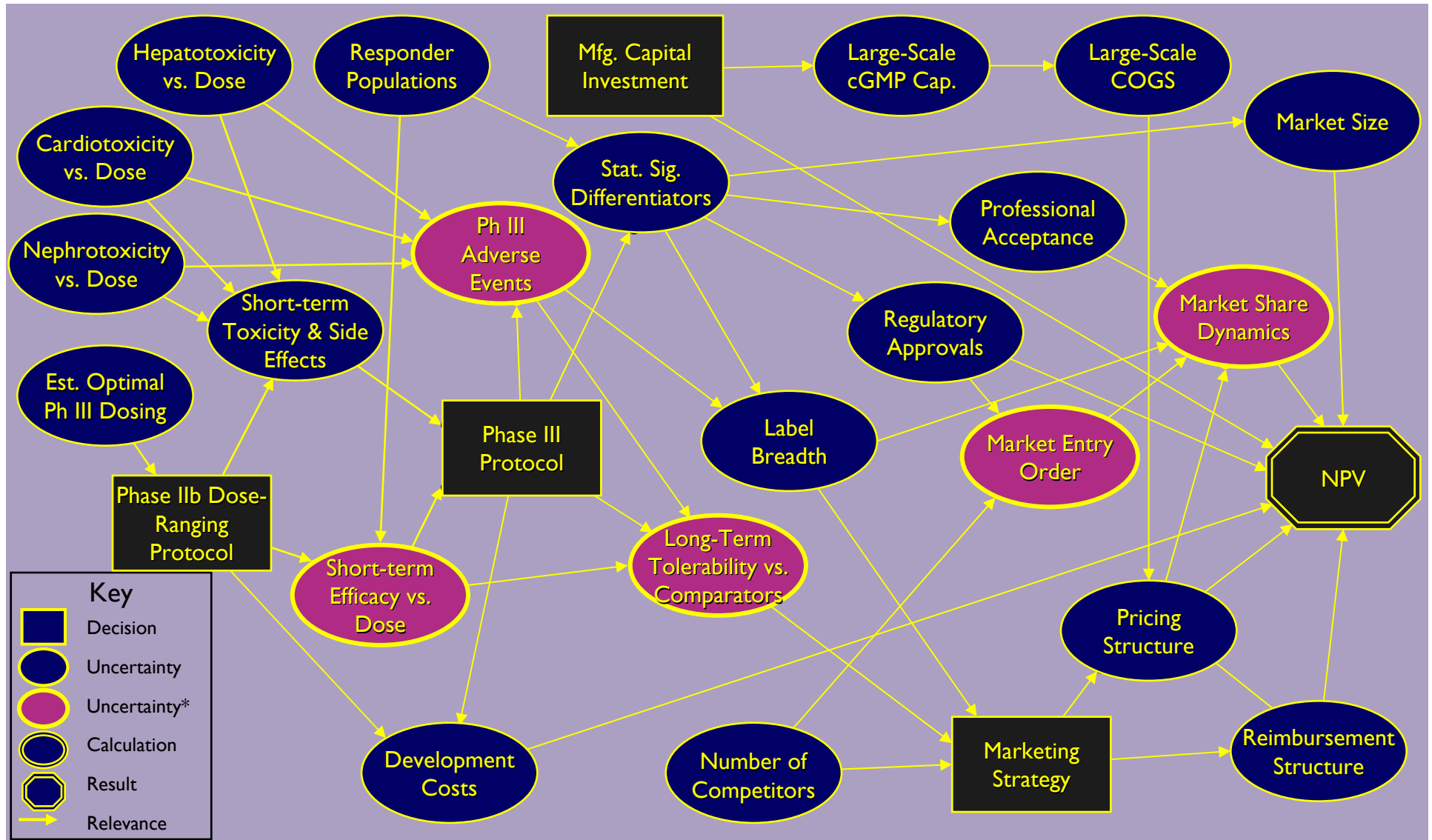
Major decisions require participation across an organization.



Typically, over 90% of project risk is due to about 20% of uncertainties.

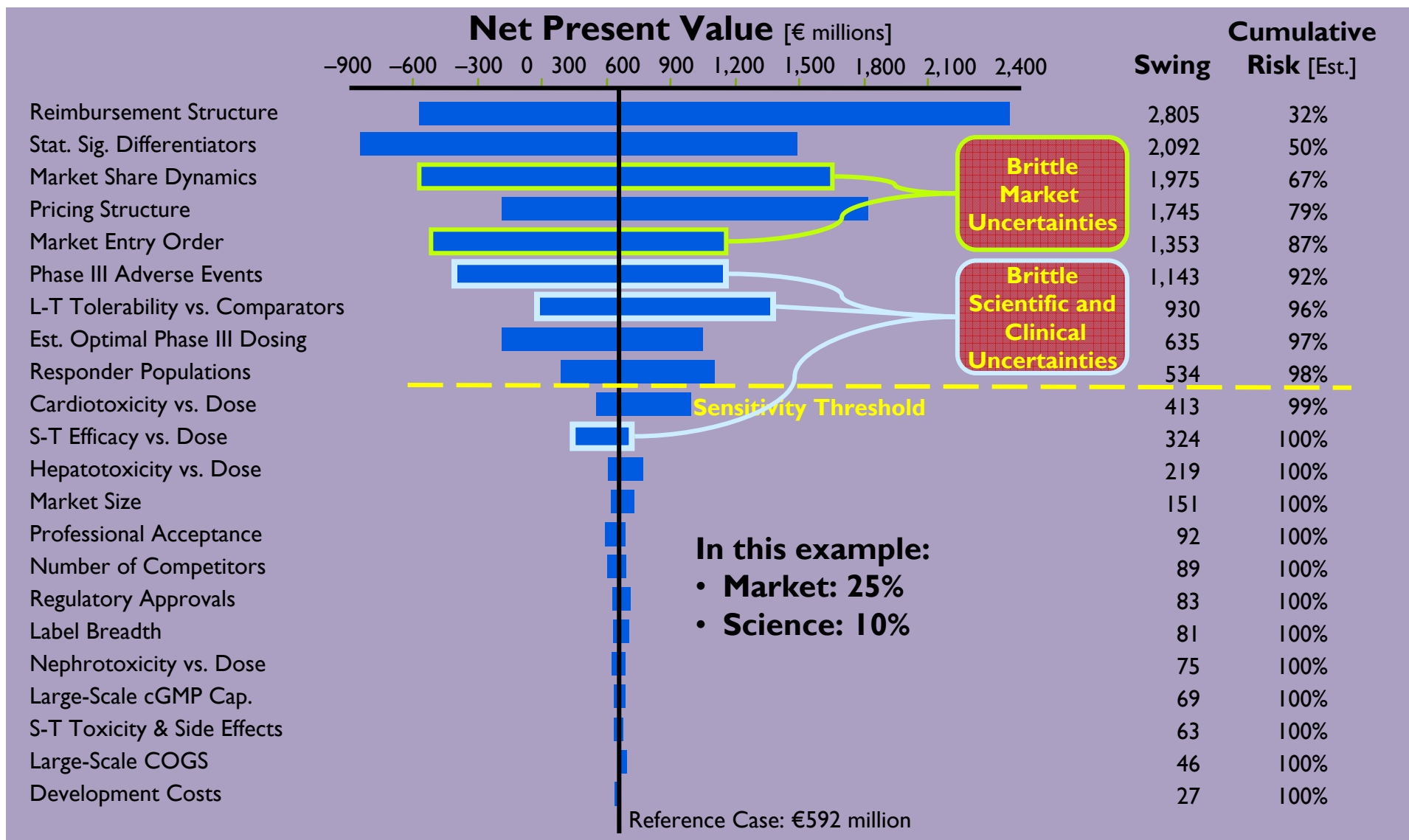


Invariably, for some key uncertainties – brittle uncertainties – there is little or no direct expertise.



* For which there is little or no direct expertise

Brittle uncertainties are the source of significant risk.



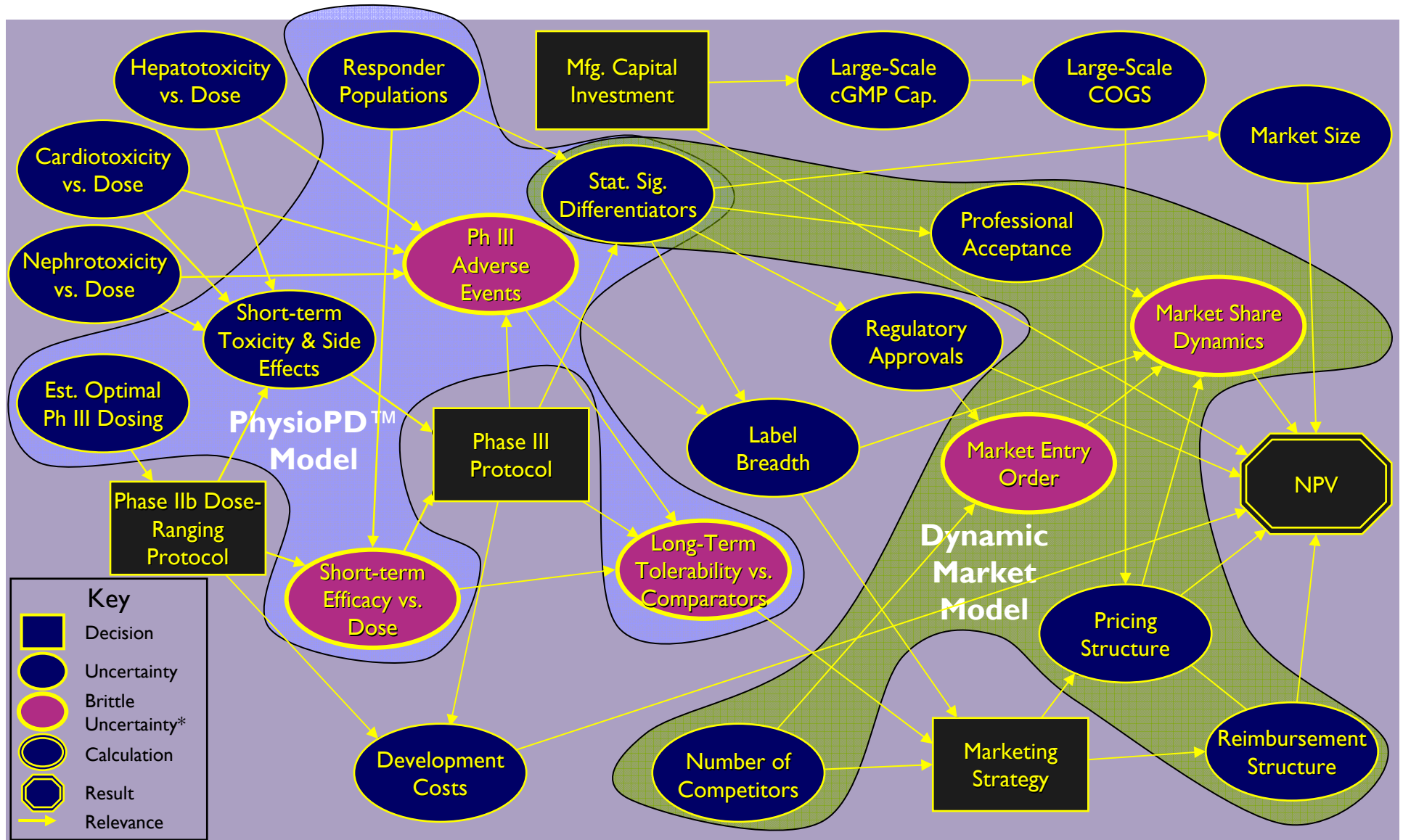
No wonder early pharmaceutical project evaluations are not taken seriously!



- No one believes early scientific or market probabilities.
- Because budgets are small, management does not worry much.
- However, decisions made early in the clinical pipeline are among the **most strategic** a pharmaceutical company makes!

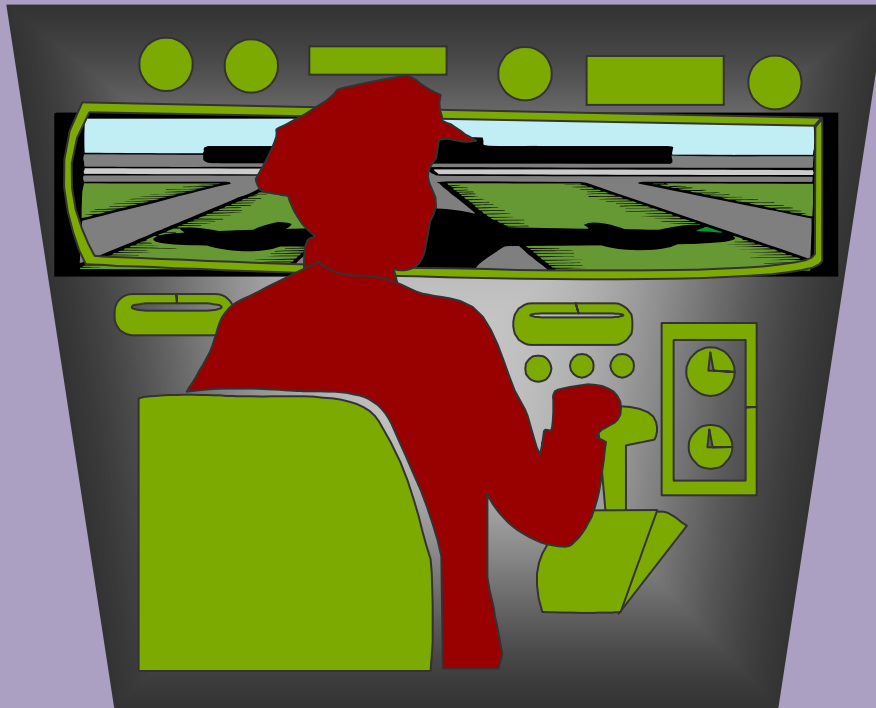


Simulation models routinely help strengthen brittle uncertainties and improve decisions.



* For which there is little or no direct expertise

Models can be used as “flight simulators” to strengthen direct expertise.



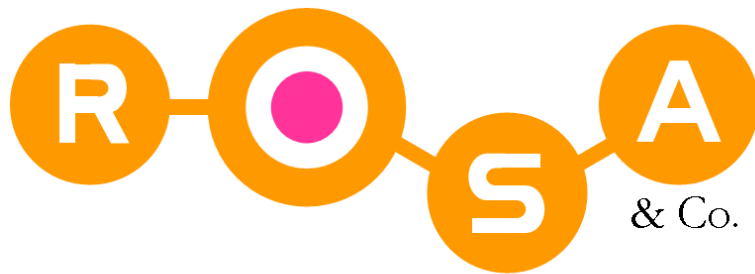
- Recent scientific/clinical uses:
 - Trial optimization (e.g., inclusion/exclusion criteria) through simulation
 - Execution of trials that in the clinic would have been too expensive, dangerous, or downright impossible.
 - Specification of optimal preclinical tests
- Recent market uses:
 - Simulation of market dynamics for alternative launch dates
 - Competitive gaming
 - Price setting
- In all cases, through “what-if” analysis researchers discovered and repaired key knowledge gaps.

The ultimate sophistication is simplicity.

- Decision-focused models are
 - Small and cost-effective
 - Custom built in weeks or a few months
 - Built collaboratively for maximum insight.
- Most of the value is in the journey.
 - Having the ideal model provides ~10% of the benefit.
 - Participating in model development provides the other ~90%.
- Modeling and simulation have wide benefits.
 - Clinical development
 - Pharmacology
 - Biostatistics
 - Marketing
 - Management

Recent Phase I Lessons from Modeling and Simulation

- Pharmacokinetics, pharmacodynamics, and toxicity can significantly differ from healthy volunteers to patients.
 - Involve diseased individuals as soon as ethically possible.
- Understanding how Phase I affects later development phases can dramatically improve Phase I design.
 - Later phases can be simulated during Phase I
 - Begin with the end in mind.
- Simulating trials that would be unethical or impossible in the clinic can greatly help anticipate safety and adverse events.



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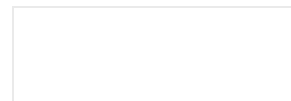
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