IDEAL
Decision Analysis (Work Package 9)

Webinar 15 November 2016

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http://www.ideal.rwth-aachen.de

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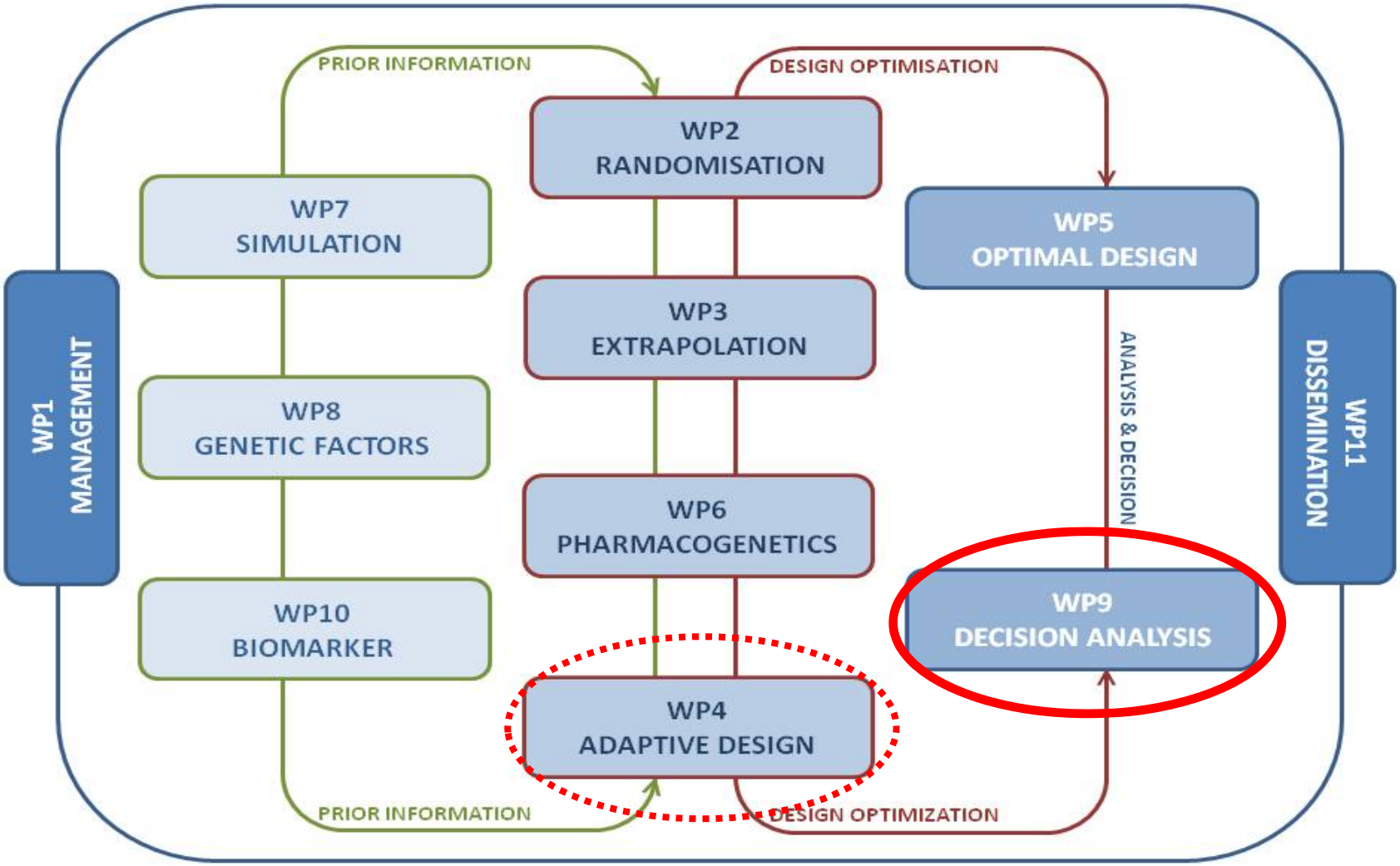
Workpackages



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Collaborators

WP 9:

- Carl-Fredrik Burman, AstraZeneca / Chalmers Univ
- Sebastian Jobjörnsson, Chalmers
- Frank Miller, Stockholm Univ
- Sören Christensen, Chalmers

EAB: Pertile, Forster

WP4: König

INSPIRE: Ondra, Posch, Stallard

DIA ADSWG: Beckman

What we're interested in

- How does (should) stakeholders make decisions on
  - Phase III investments
  - Study design
  - Market authorisation
  - Reimbursement
  - (Prescription, taking the drug)
- Can different stakeholders be aligned?

- Rare diseases and orphan drugs
- Subpopulations

Mixing scientific perspectives

- Pharmaceutical statistics
  - Frequentist hypothesis testing, power
- Bayesian decision theory
  - Priors, explicit goal functions
- Economics
  - ”rational” agents, mechanism design

GENERIC MODEL

Generic abstract model

D_s

Sponsor's decision regarding Phase III

- Go / No Go
- Sample size, n
- (Sub)population(s)
- Testing strategy
- Dose(s)
- Etc.

Trial outcome

$D_s \rightarrow X$

Data from the Phase III trial (programme)

- This is a random (multi-dimensional) variable
- Efficacy
- Safety

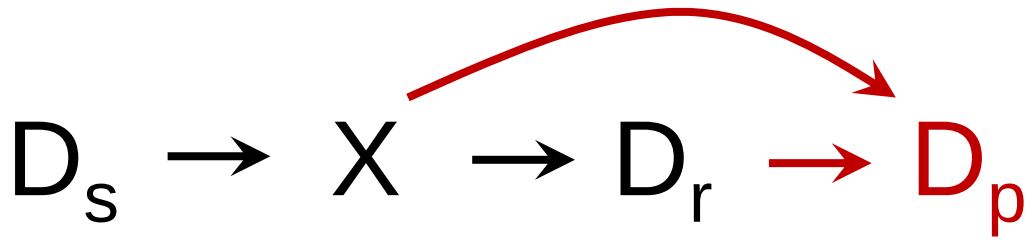
Regulatory decision

$$D_s \rightarrow X \rightarrow D_r$$

Marketing authorization decision by the regulatory agency (RA)

- Often approximated as zero/one decision (approve / non-approve)
- … but may be qualified / restricted to a subpopulation
- Depends implicitly also on design.
- Could be different in different regions.

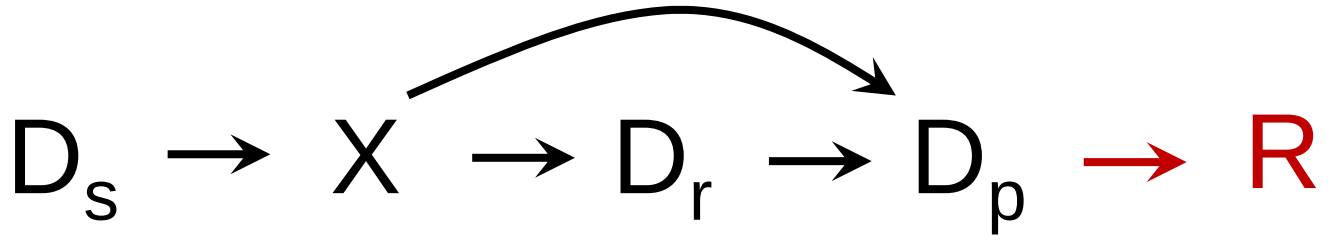
Payer decision



Payer decision

- Reimburse?
- Which price to accept?
  - E.g. UK's NICE has policy to pay per QaLY
- For which subpopulation(s)
- Multiple payers

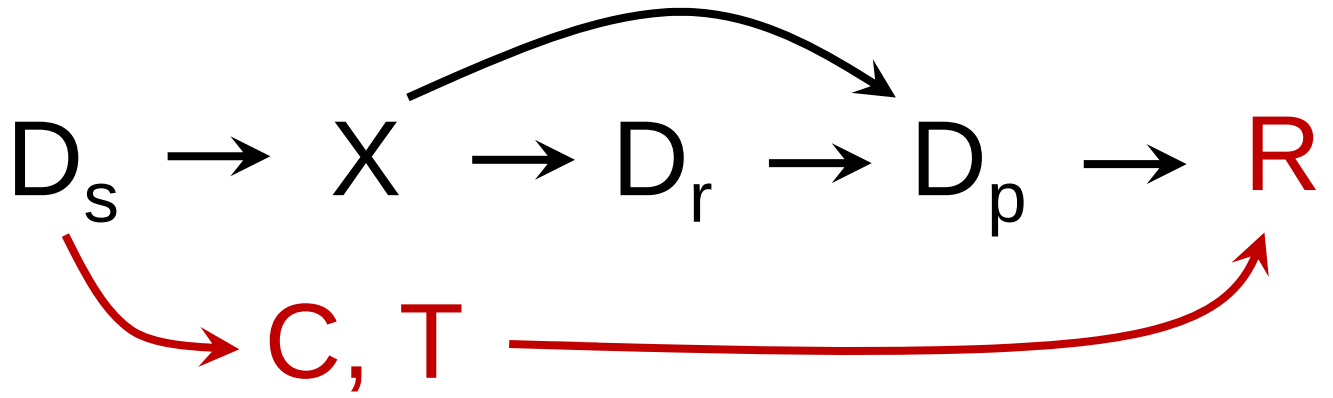
Sponsor's reward



The sponsor receives a reward if the drug is approved and reimbursed

- Depends on price
- And (sub)population
  - This size of the population is of special interest to IDEAL

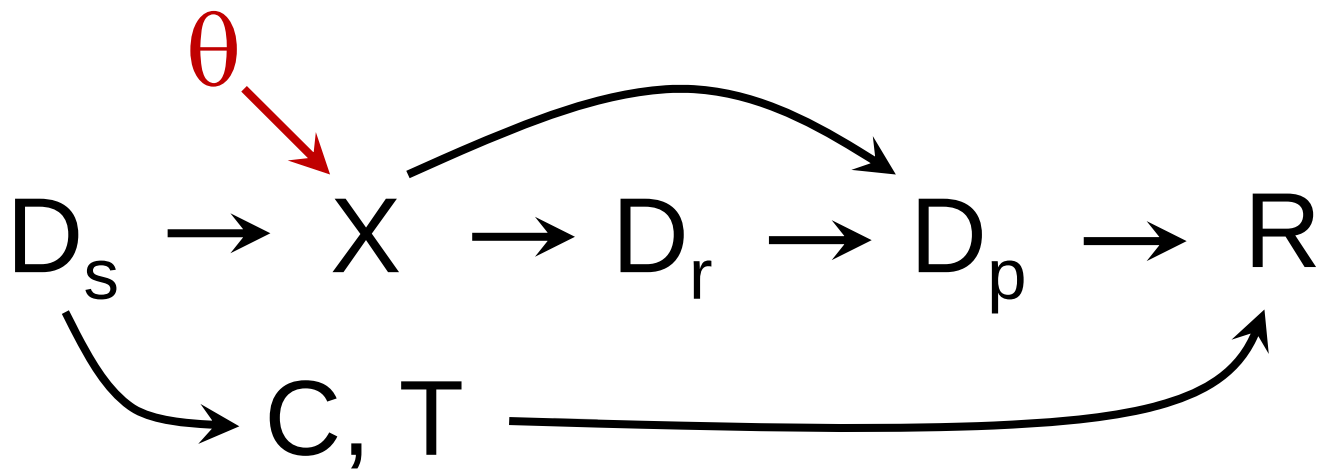
Sponsor's reward



The net reward also depends on costs and time to market

- Sample size, n
- Cost C=C(n)
- Time T=T(n)

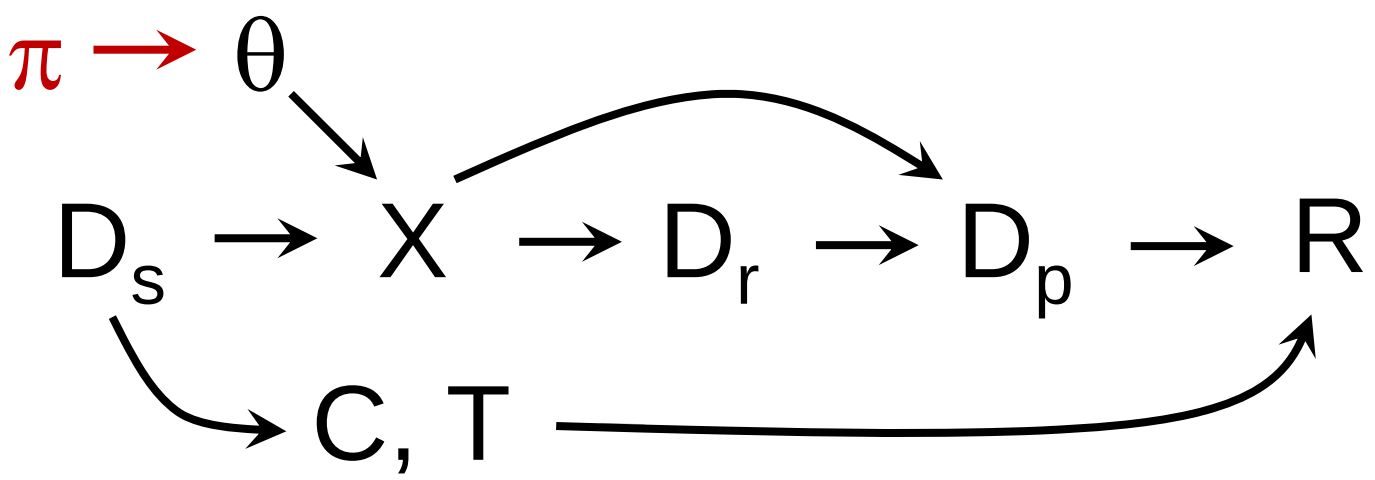
The parameter



The true properties of the drug is captured in the parameter

- Efficacy
- Safety
- Multi-dimensional
- May depend on subpopulation or other covariates
- … and the dose

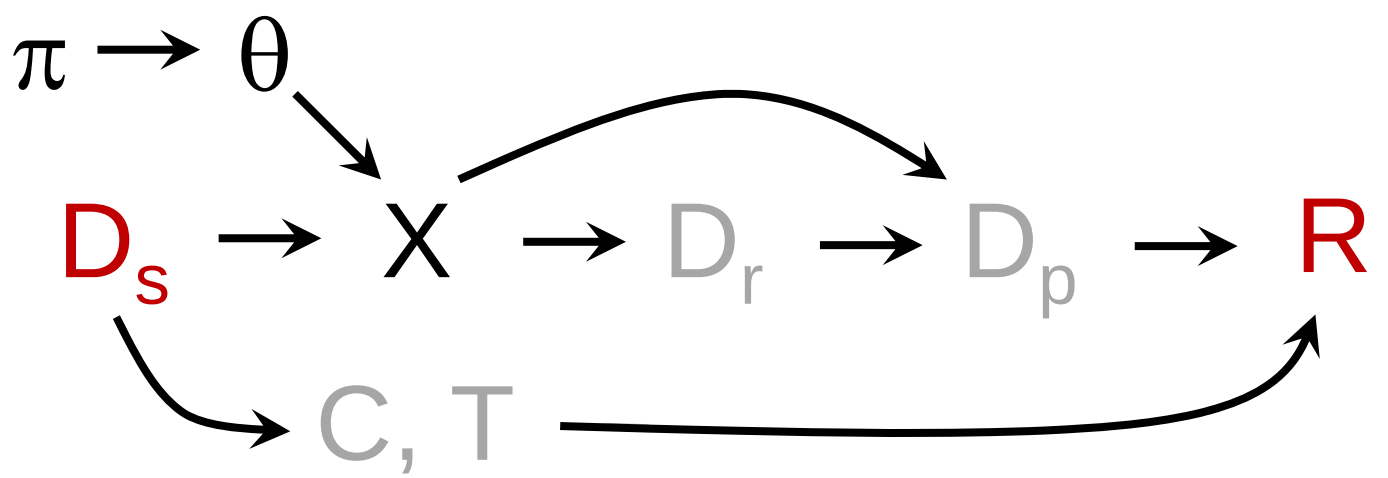
Let's be Bayesian



The parameter follows a prior distribution

- The sponsor has to base its decision on some prior information
- This is formalized as a Bayesian prior
- Choosing a 1-point prior means fixing θ
- The Bayesian approach may or may not be used by different stakeholders. May use different priors.

Optimizing the Phase III investment decision



- Take the RA and payer rules as fixed.
- Sponsor's expected reward

  $ER(D_s)$
- Optimal decision

  $D_s^* = \text{argmax}_{Ds}\ ER(D_s)$

Optimal sample size

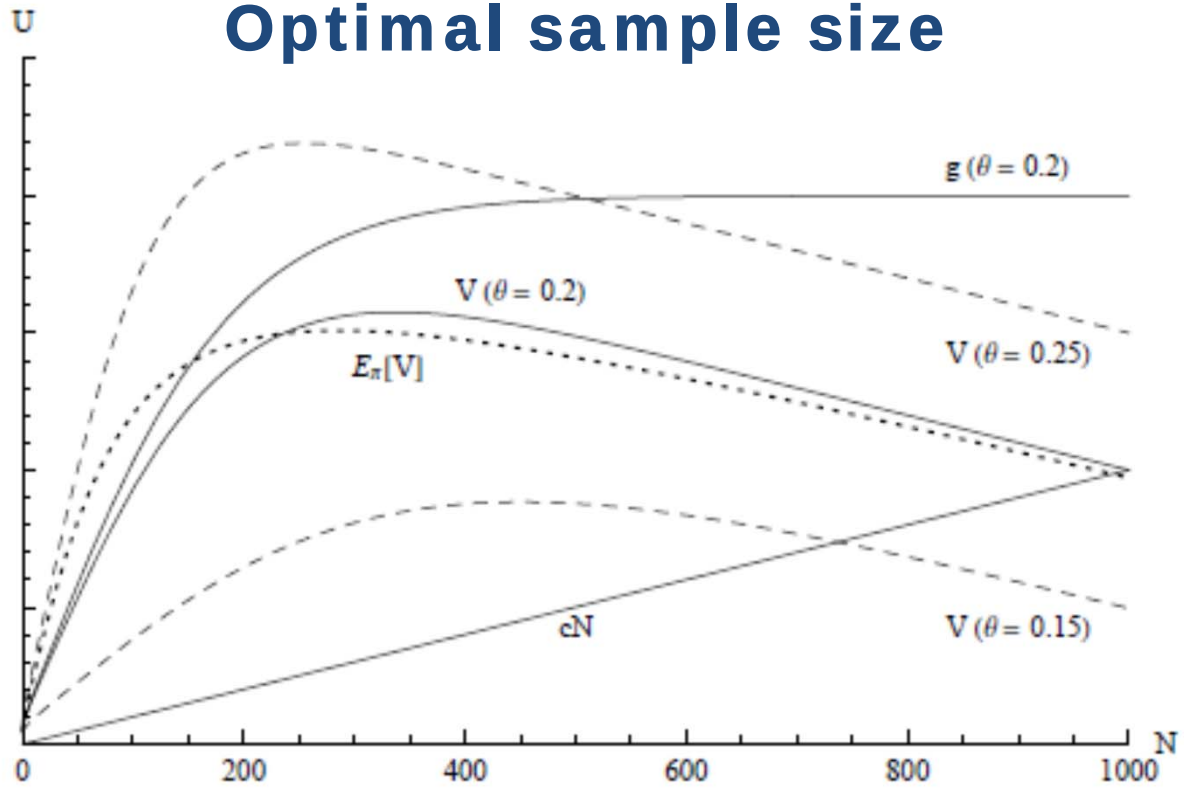
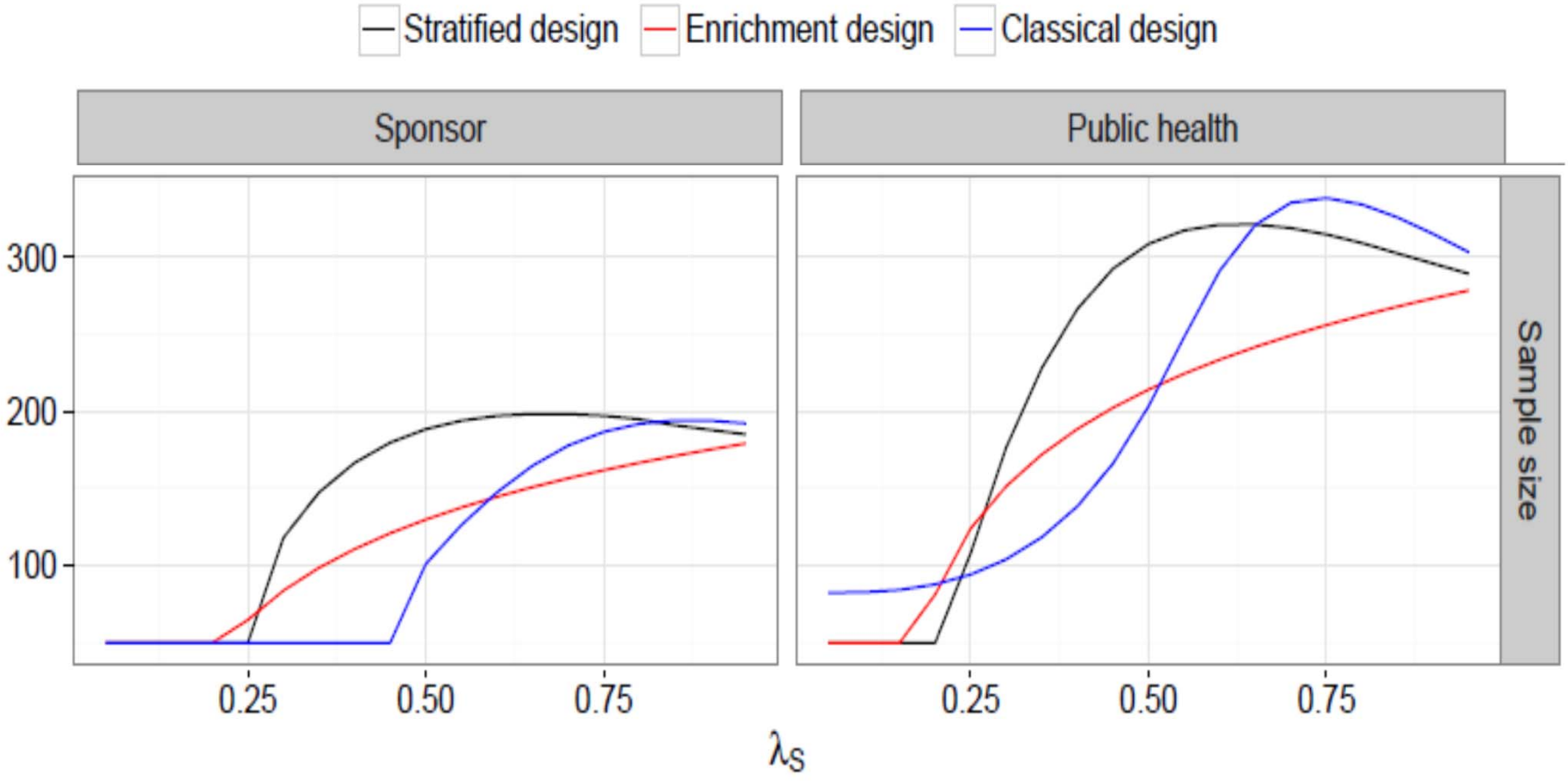
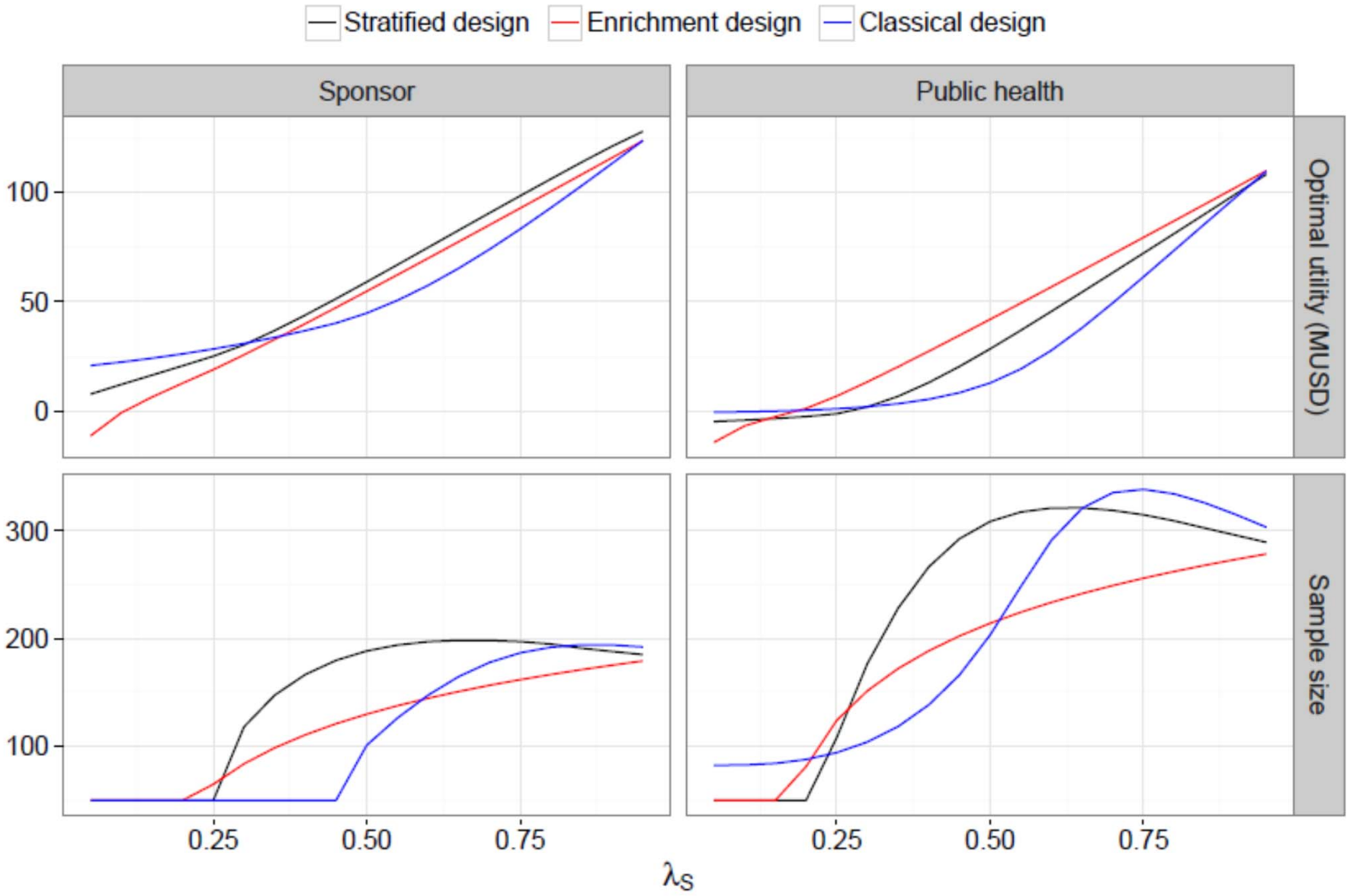


Figure 2: *The utility function for some specific values of θ, and when θ follows a Normal$(0.2; 0.1)$ prior. Solid lines show the cost, expected gain $g = k\,\theta\,p(N, \theta)$ and expected net utility $V = E[U(N, \theta)]$ when $\theta = 0.2$. Dashed lines indicate a higher/lower utility if θ is higher/lower. The dotted line gives the expected utility over the prior for θ.*

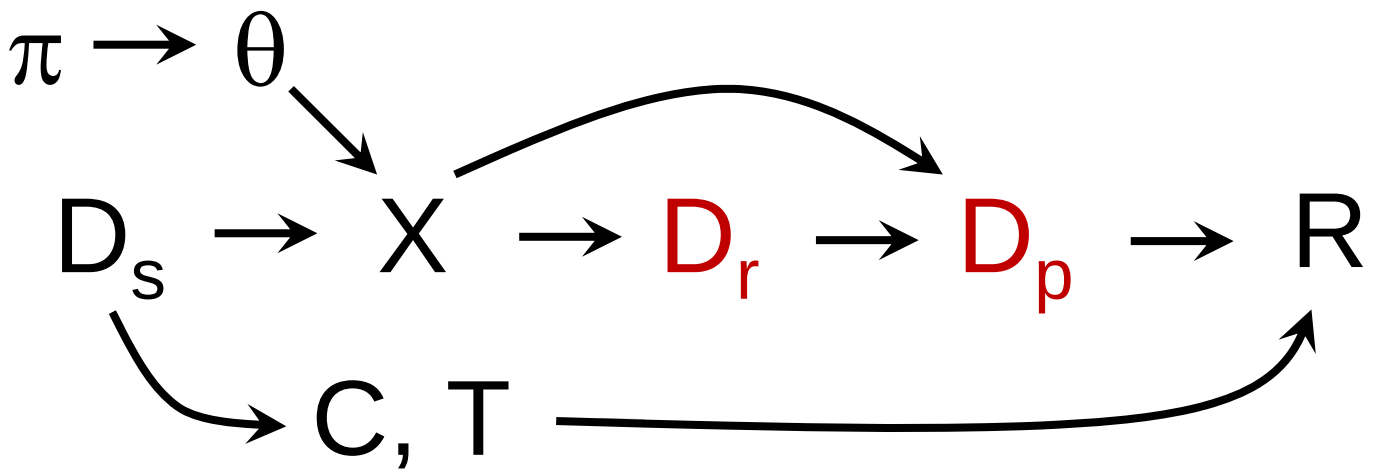
Biomarker-defined subpopulations



Biomarker-defined subpopulations



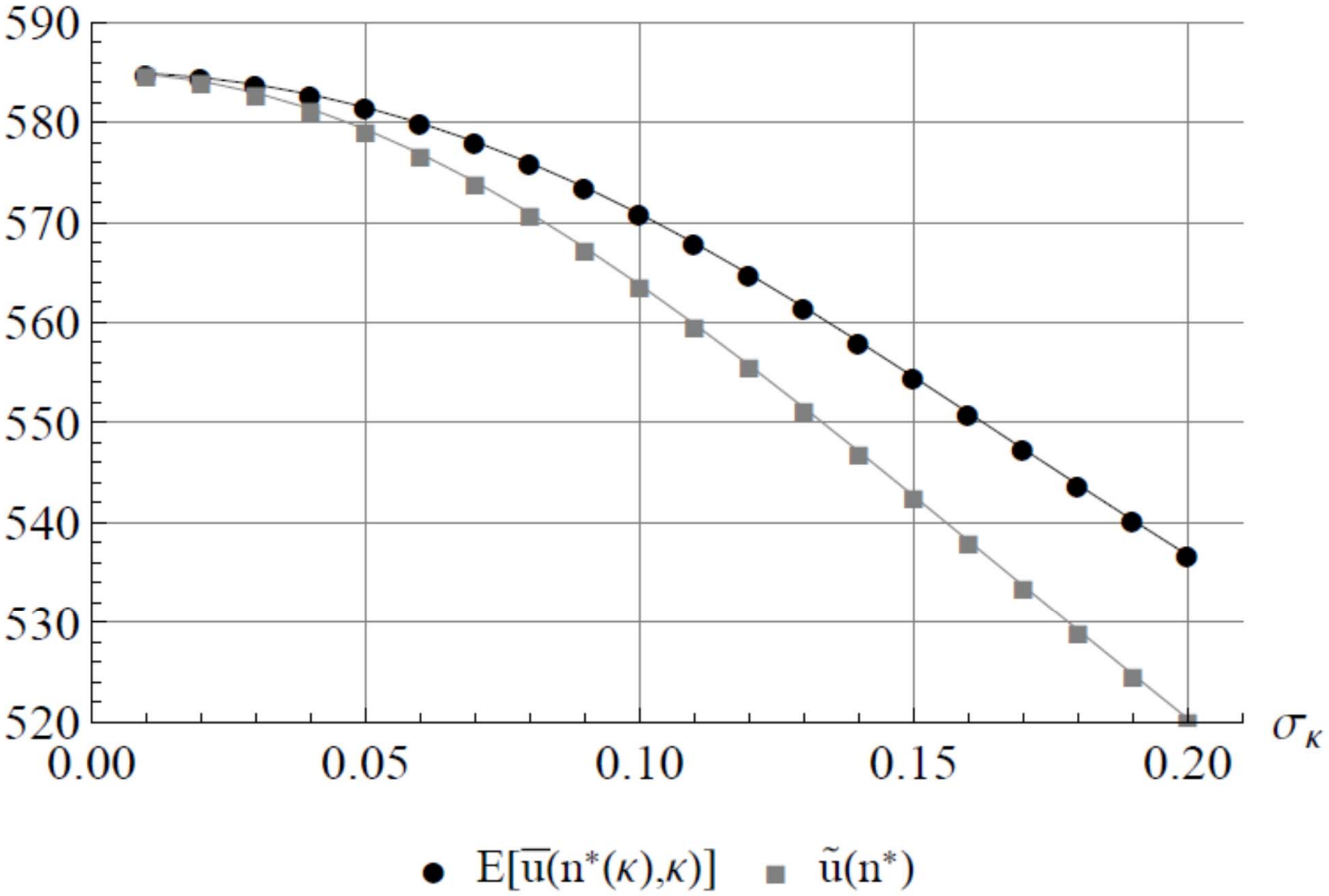
Uncertain regulatory / payer decision rules



If the regulatory rule is not clearly stated?

- The sponsor has to use a prior for the rule
- What is the probability of acceptance for a certail data set?
- Such in-transparency invokes a cost for sponsors and for the patients
- Some useful drugs may never be tested in Phase III

Value as a function of uncertainty



Pricing in the face of uncertainty

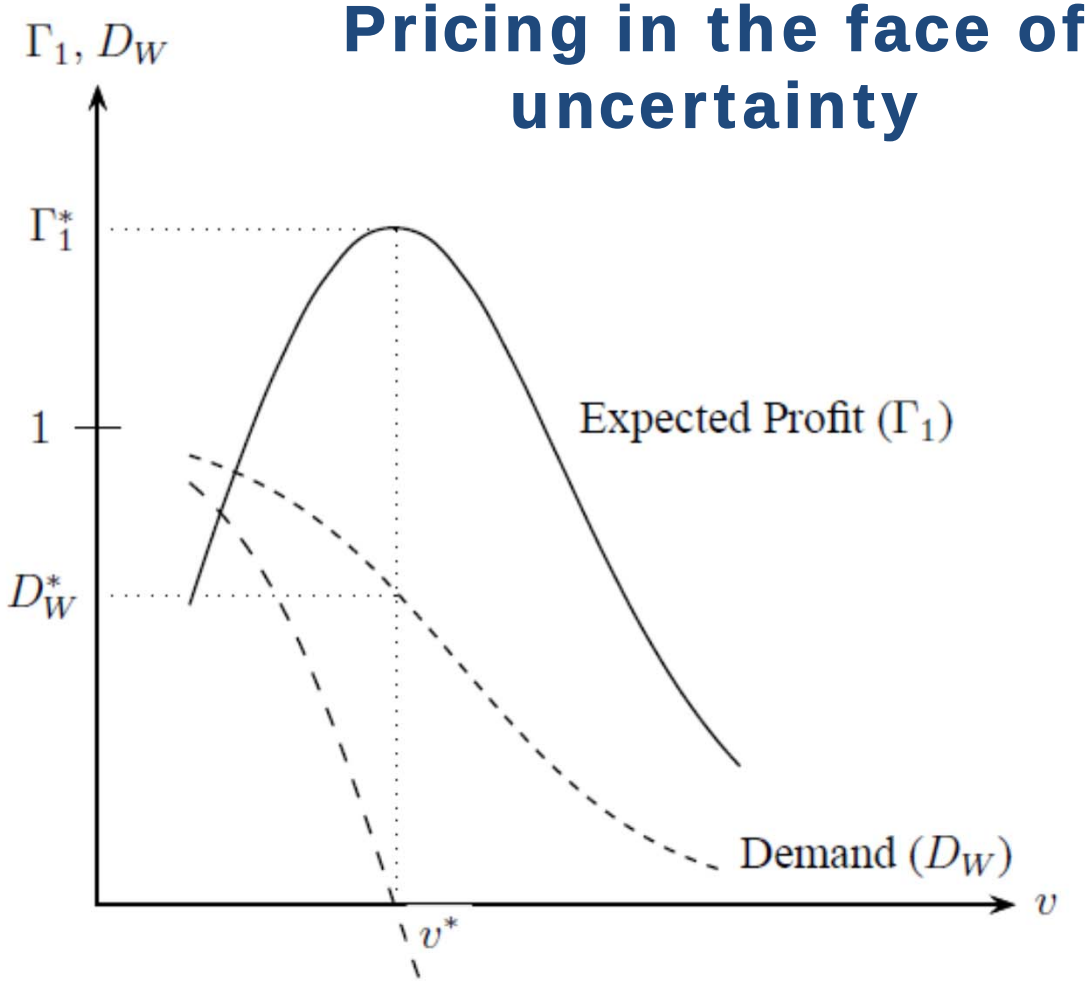
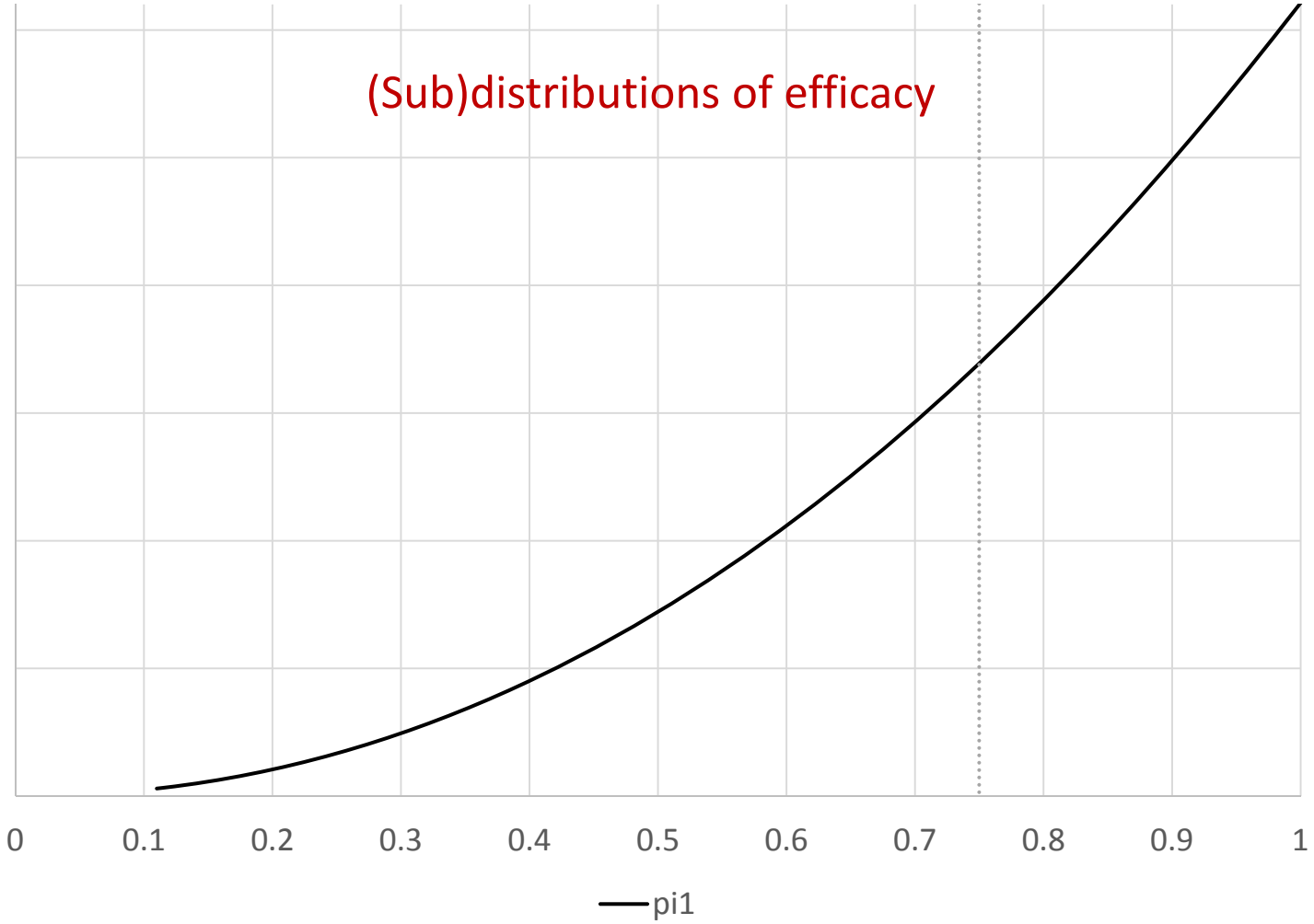
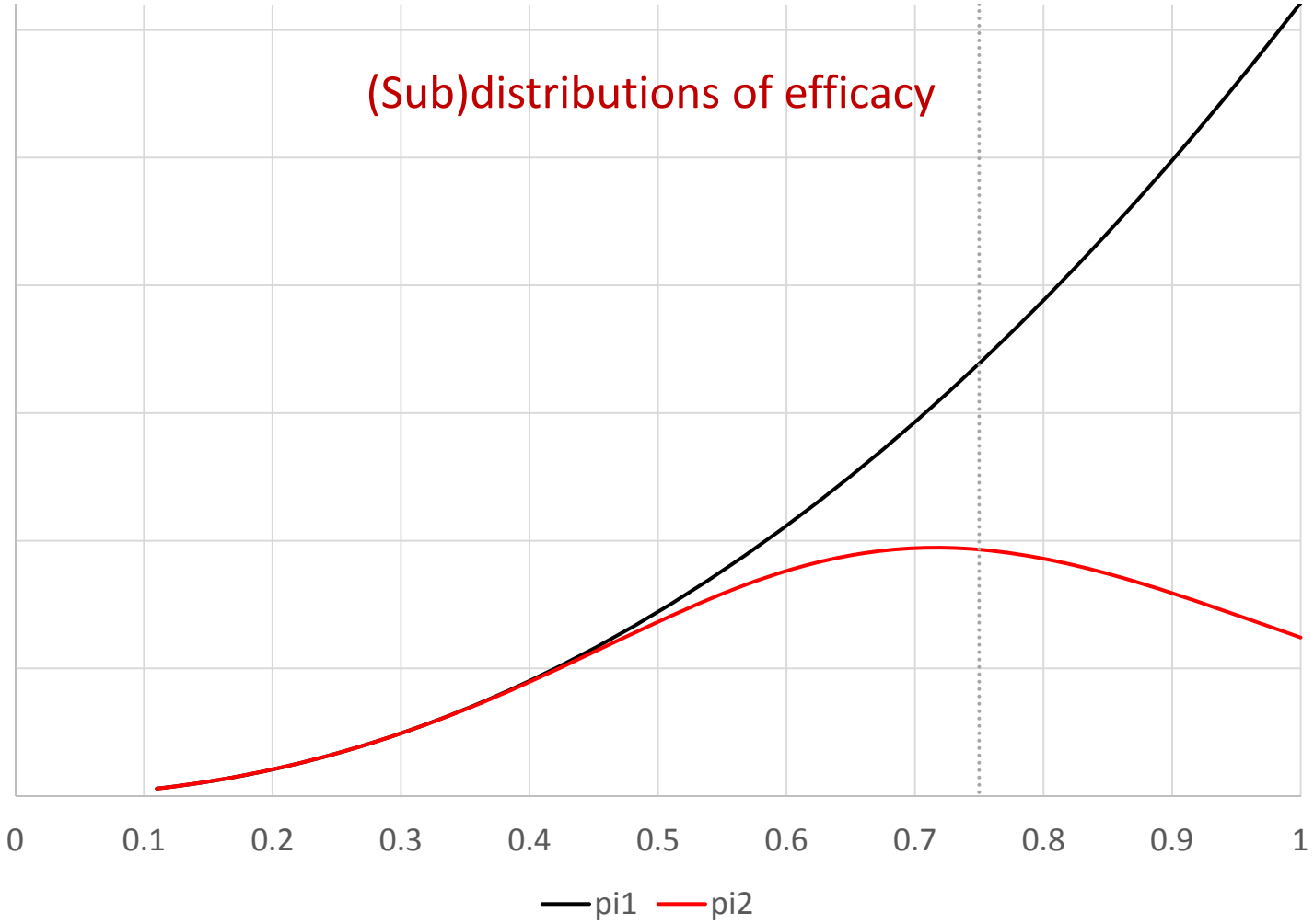


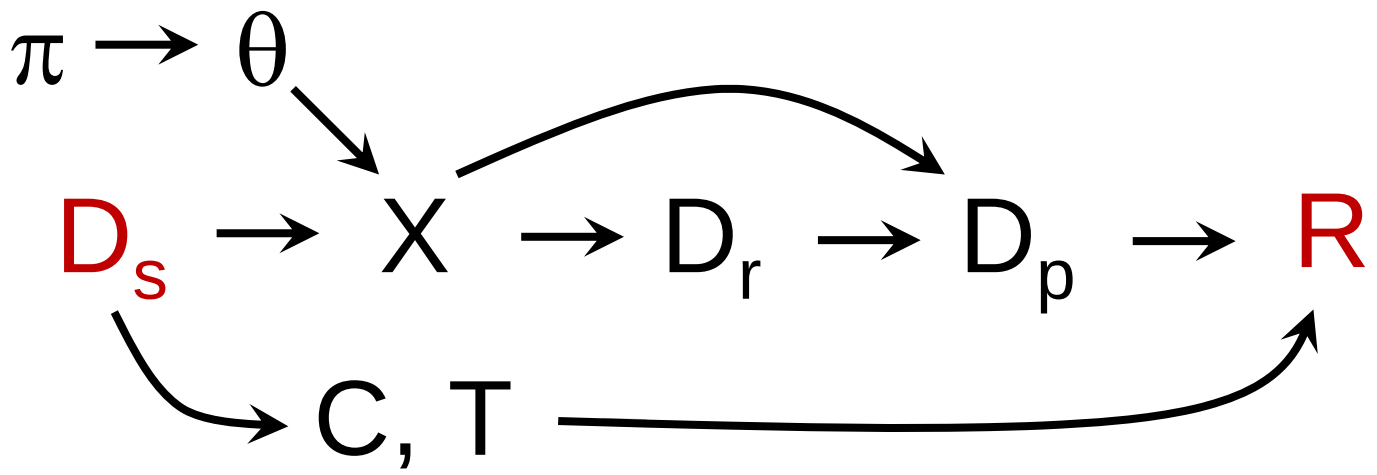
Figure 2: Expected profit function (Eq. (5), continuous line), expected demand function $D_W(\cdot) \equiv 1 - F_W(v; m, s)$ (short dash) and the LHS of Eq. (6) (long dash) showing the optimal choice of the ICER, v^*.

MECHANISM DESIGN


(Sub)distributions of efficacy
0
0.1
0.2
0.3
0.4
0.5
0.6
0.7
0.8
0.9
1
pi1


(Sub)distributions of efficacy
0
0.1
0.2
0.3
0.4
0.5
0.6
0.7
0.8
0.9
1
pi1
pi2

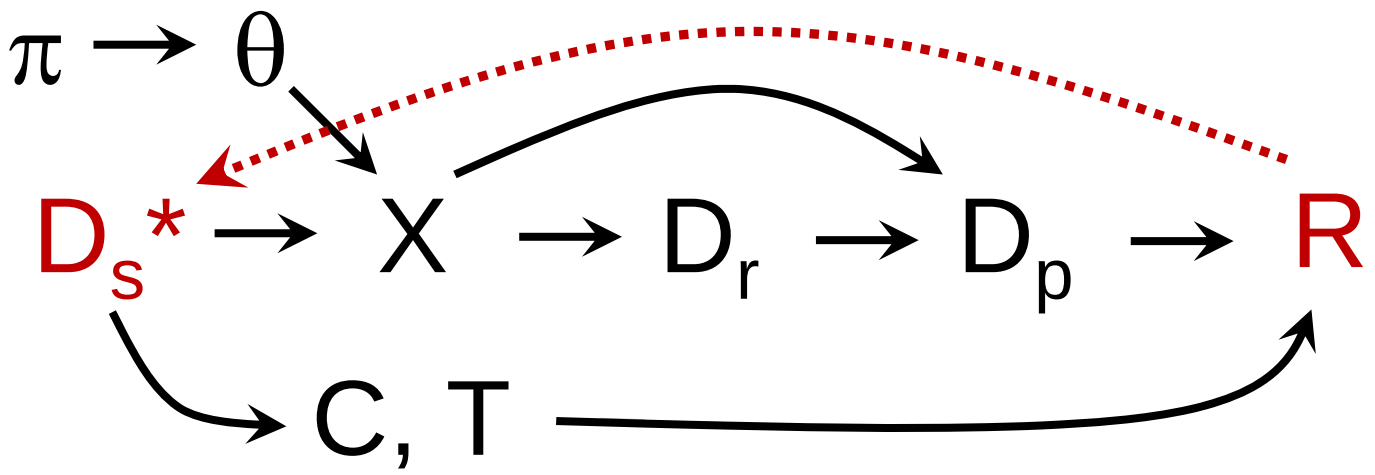
Optimal sponsor decision



- Optimal sponsor decision

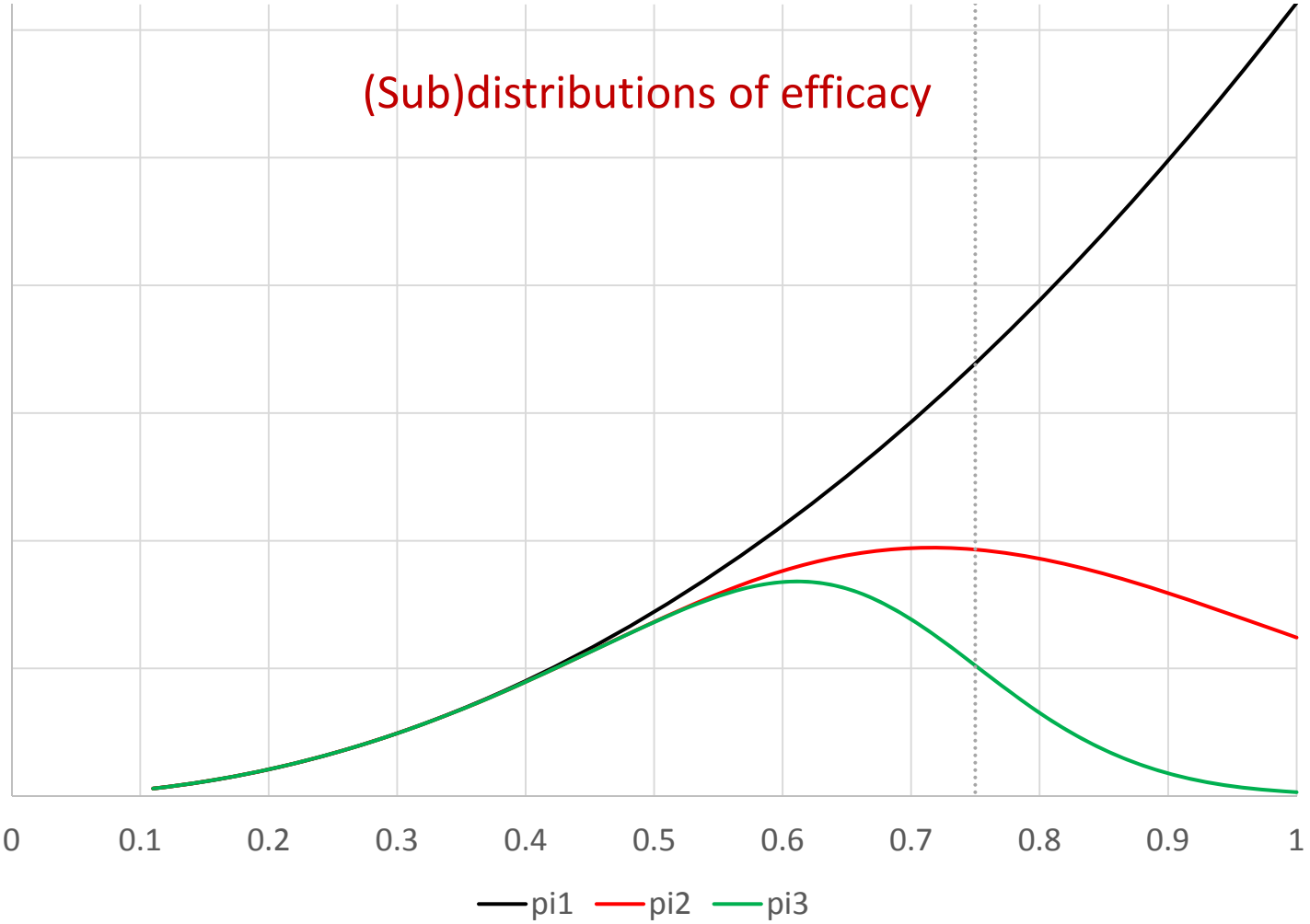
$$D_s^* = \text{argmax}_{Ds}\ ER(D_s)$$

Optimal sponsor decision

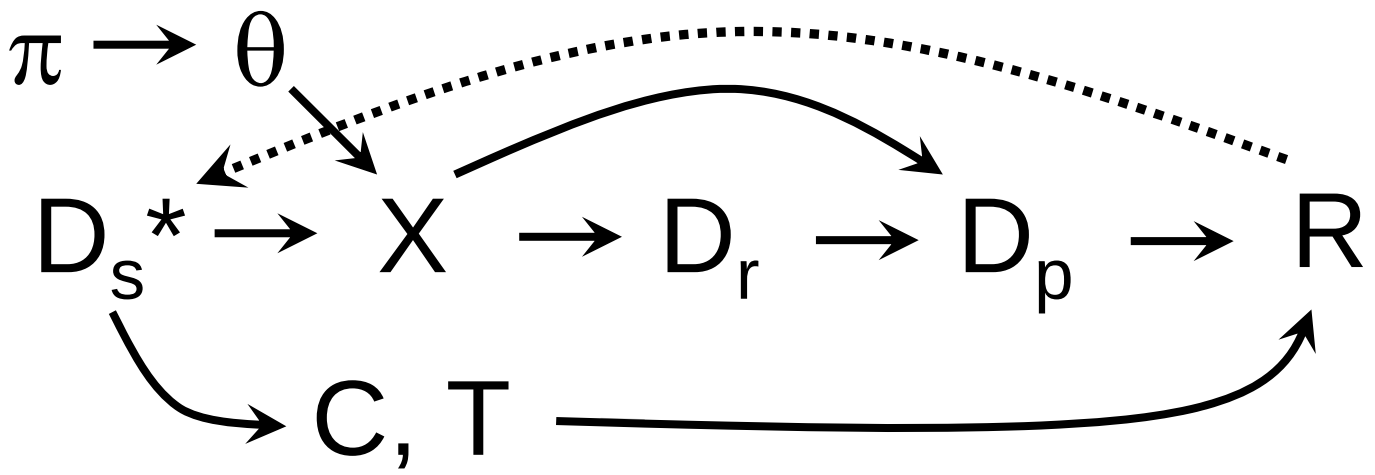


- Optimal sponsor decision

$$D_s^* = \text{argmax}_{Ds}\ ER(D_s, D_r, D_p)$$


(Sub)distributions of efficacy
0
0.1
0.2
0.3
0.4
0.5
0.6
0.7
0.8
0.9
1
pi1
pi2
pi3

Optimal sponsor decision



- Optimal sponsor decision

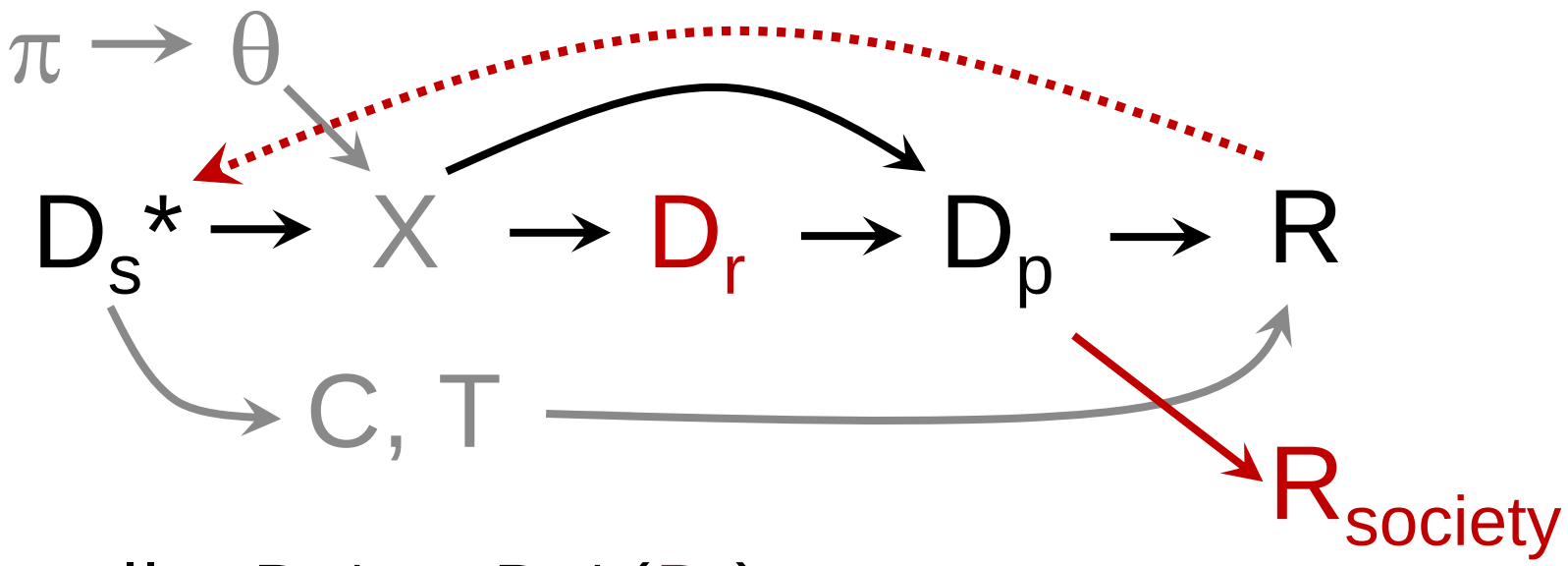
$$D_s^* = \text{argmax}_{Ds}\, ER(D_s, D_r, D_p)$$

- Note that

$$D_s^* = D_s^*(D_r, D_p)$$

- For simplicity, focus on D_r but not D_p

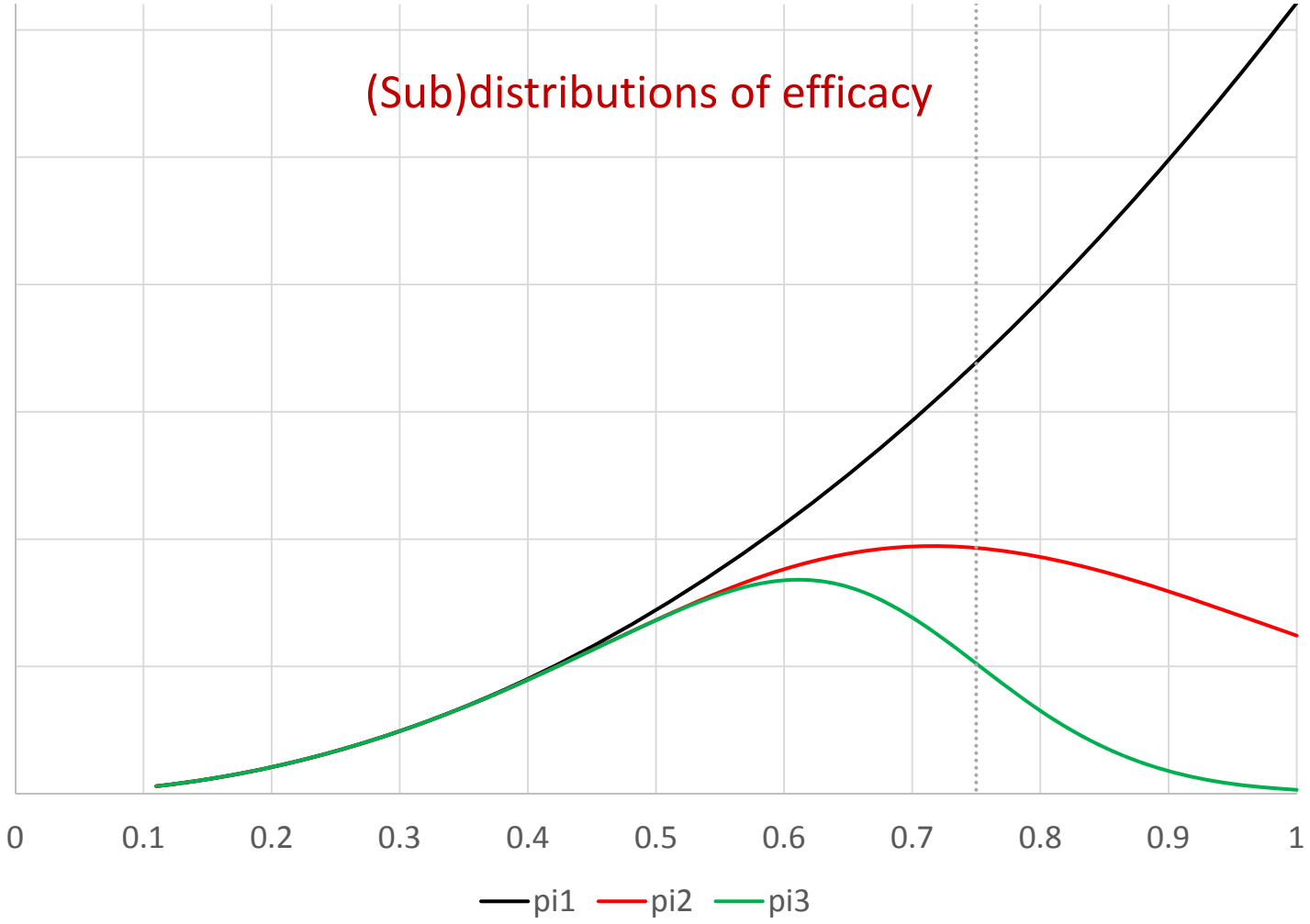
How to optimally choose the regulatory rule?

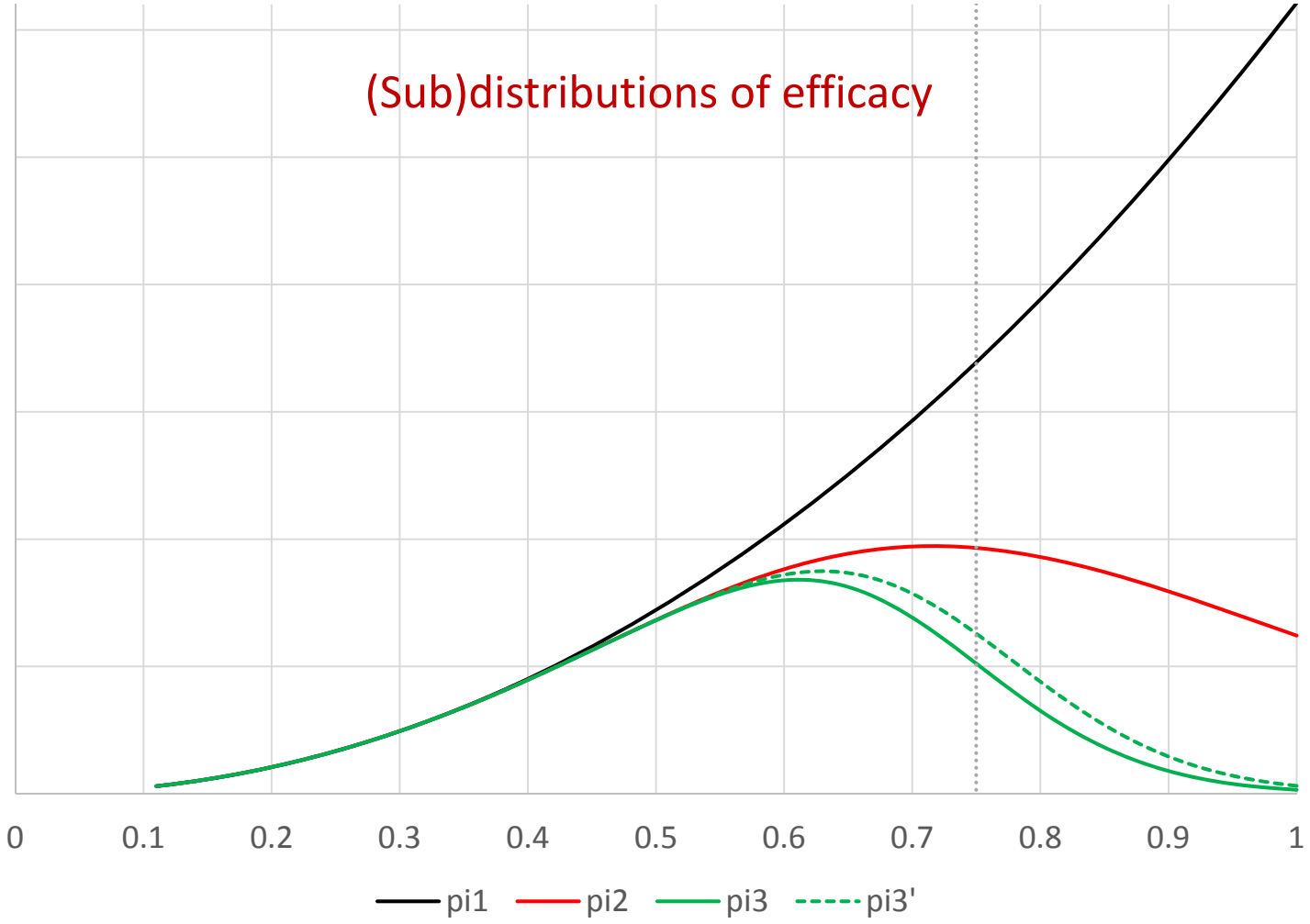


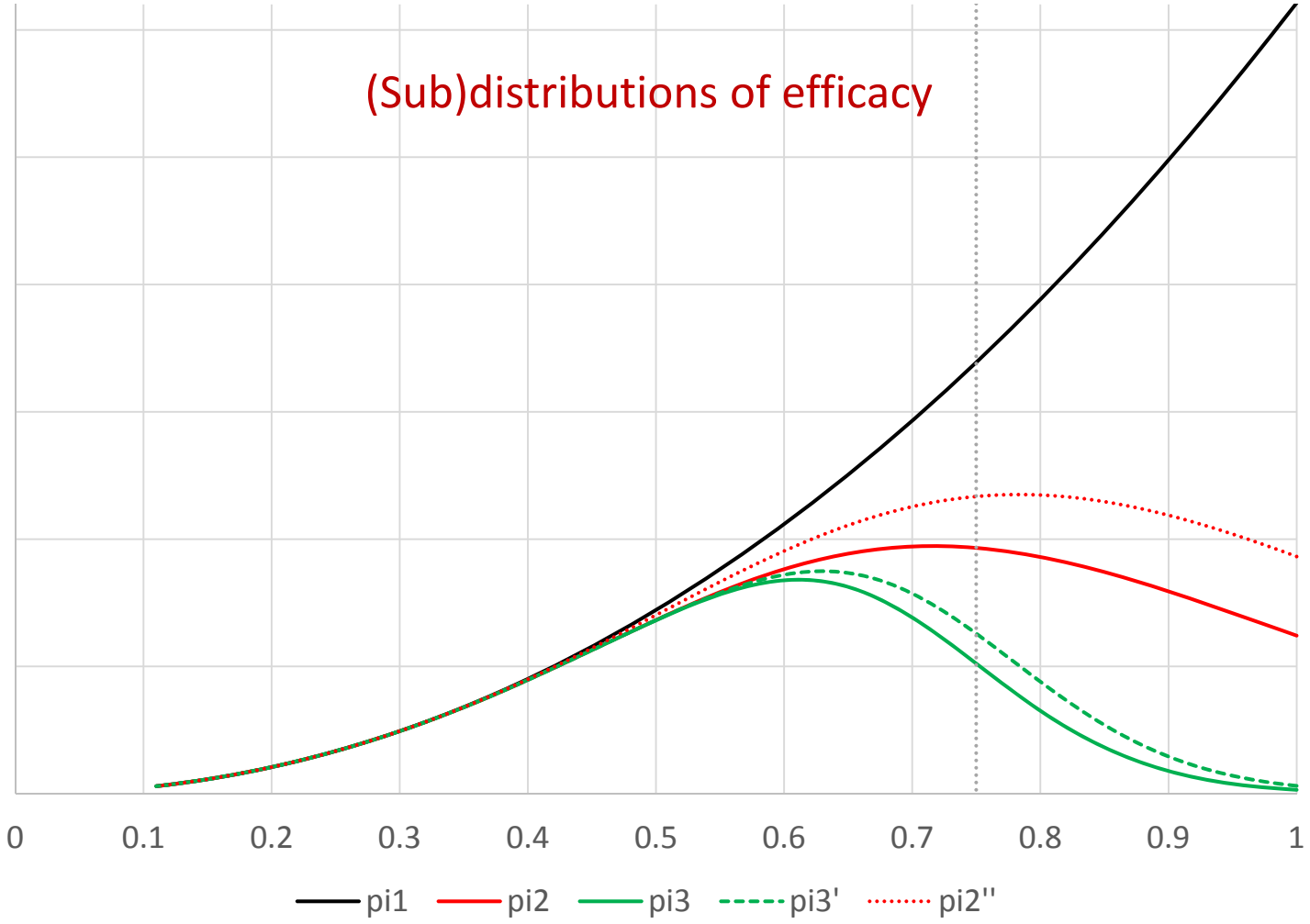
- Recall $D_s^* = D_s^*(D_r)$
- Expected societal value

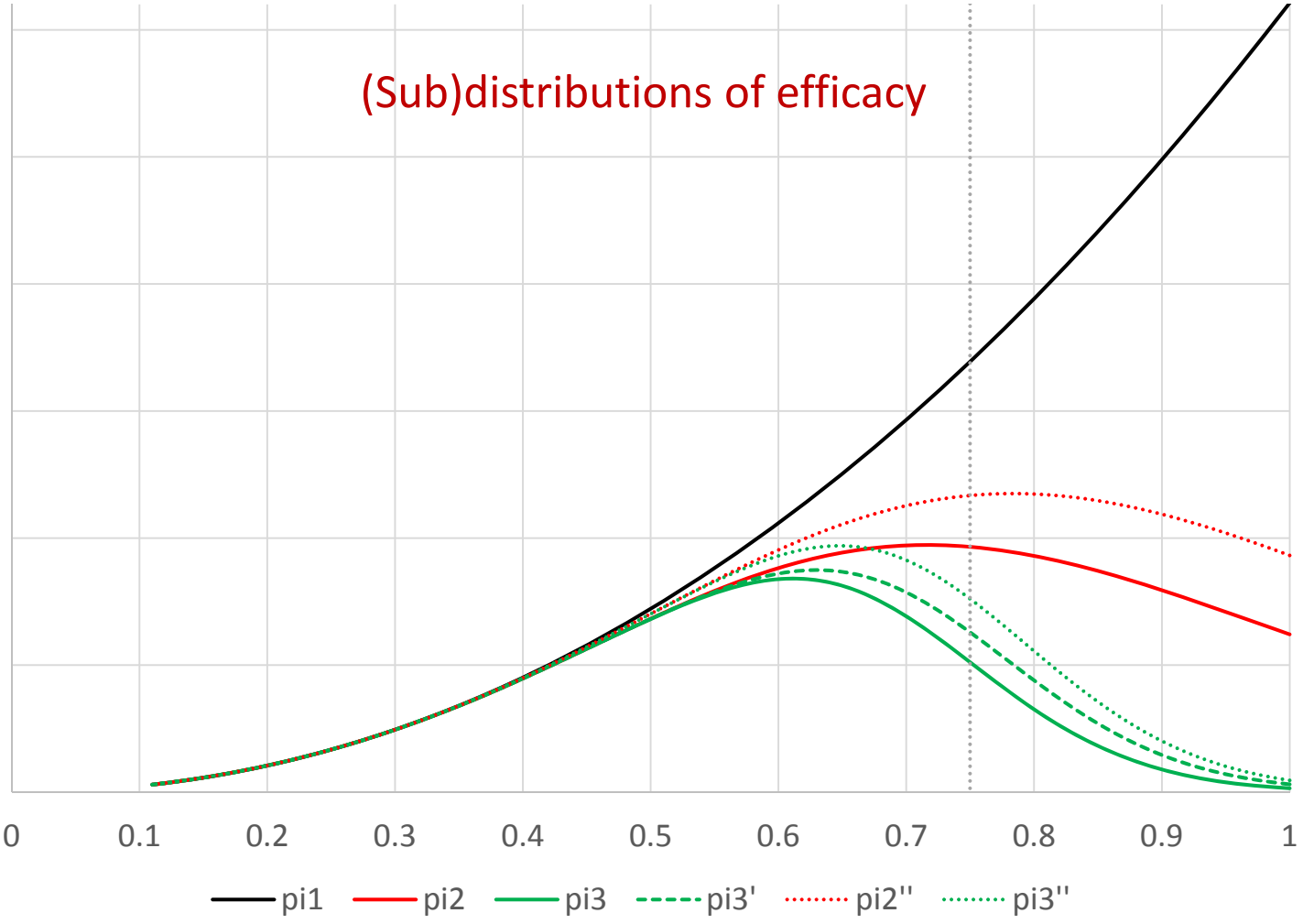
$$ER_{society}(D_s^*(D_r), D_r)$$

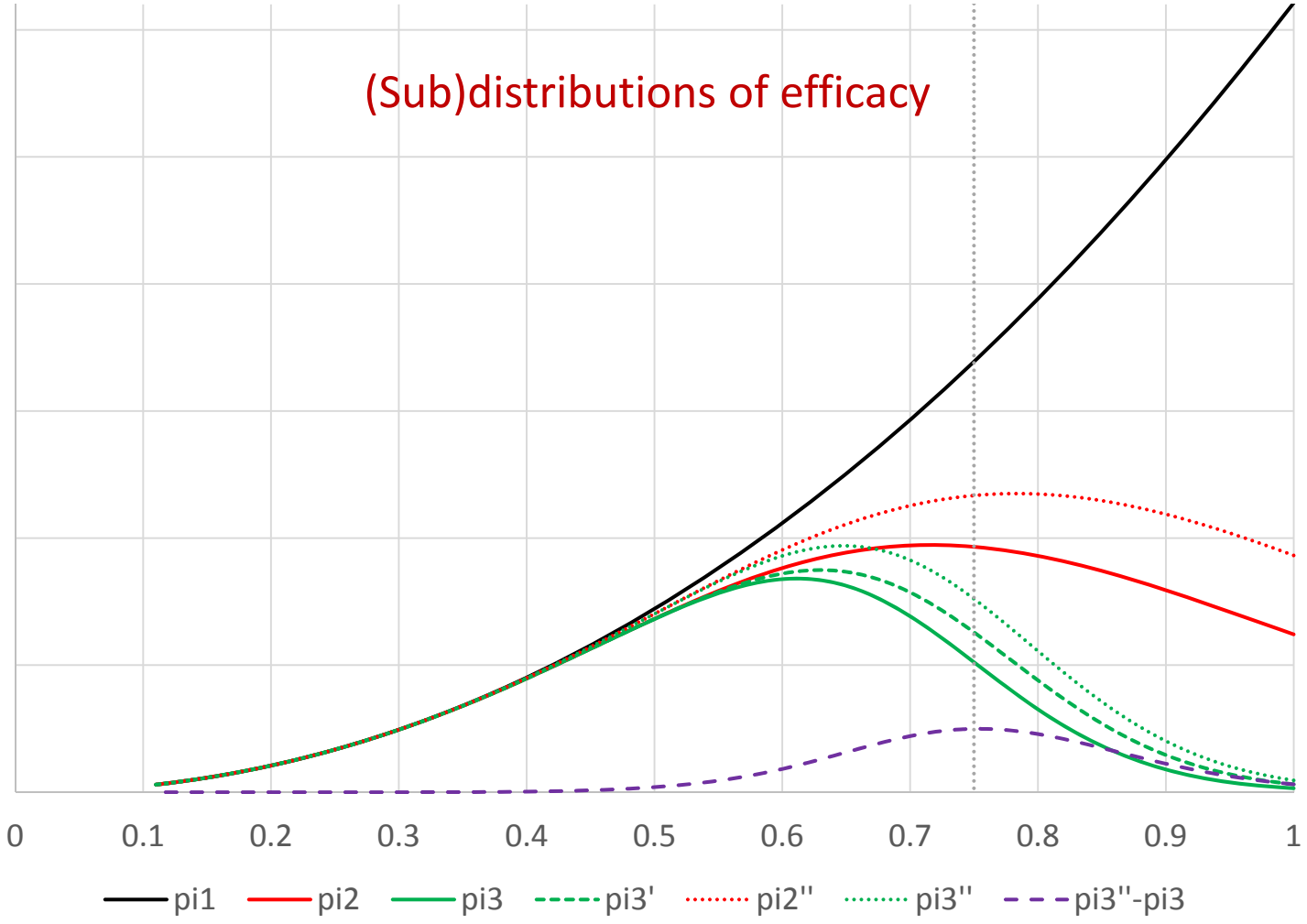
- Choose optimal D_r^* to get maximal expected societal value


(Sub)distributions of efficacy
0
0.1
0.2
0.3
0.4
0.5
0.6
0.7
0.8
0.9
1
pi1
pi2
pi3


(Sub)distributions of efficacy
0
0.1
0.2
0.3
0.4
0.5
0.6
0.7
0.8
0.9
1
pi1
pi2
pi3
pi3'


(Sub)distributions of efficacy
0
0.1
0.2
0.3
0.4
0.5
0.6
0.7
0.8
0.9
1
pi1
pi2
pi3
pi3'
pi2''


(Sub)distributions of efficacy
0
0.1
0.2
0.3
0.4
0.5
0.6
0.7
0.8
0.9
1
pi1
pi2
pi3
pi3'
pi2''
pi3''


(Sub)distributions of efficacy
0
0.1
0.2
0.3
0.4
0.5
0.6
0.7
0.8
0.9
1
pi1
pi2
pi3
pi3'
pi2''
pi3''
pi3''-pi3

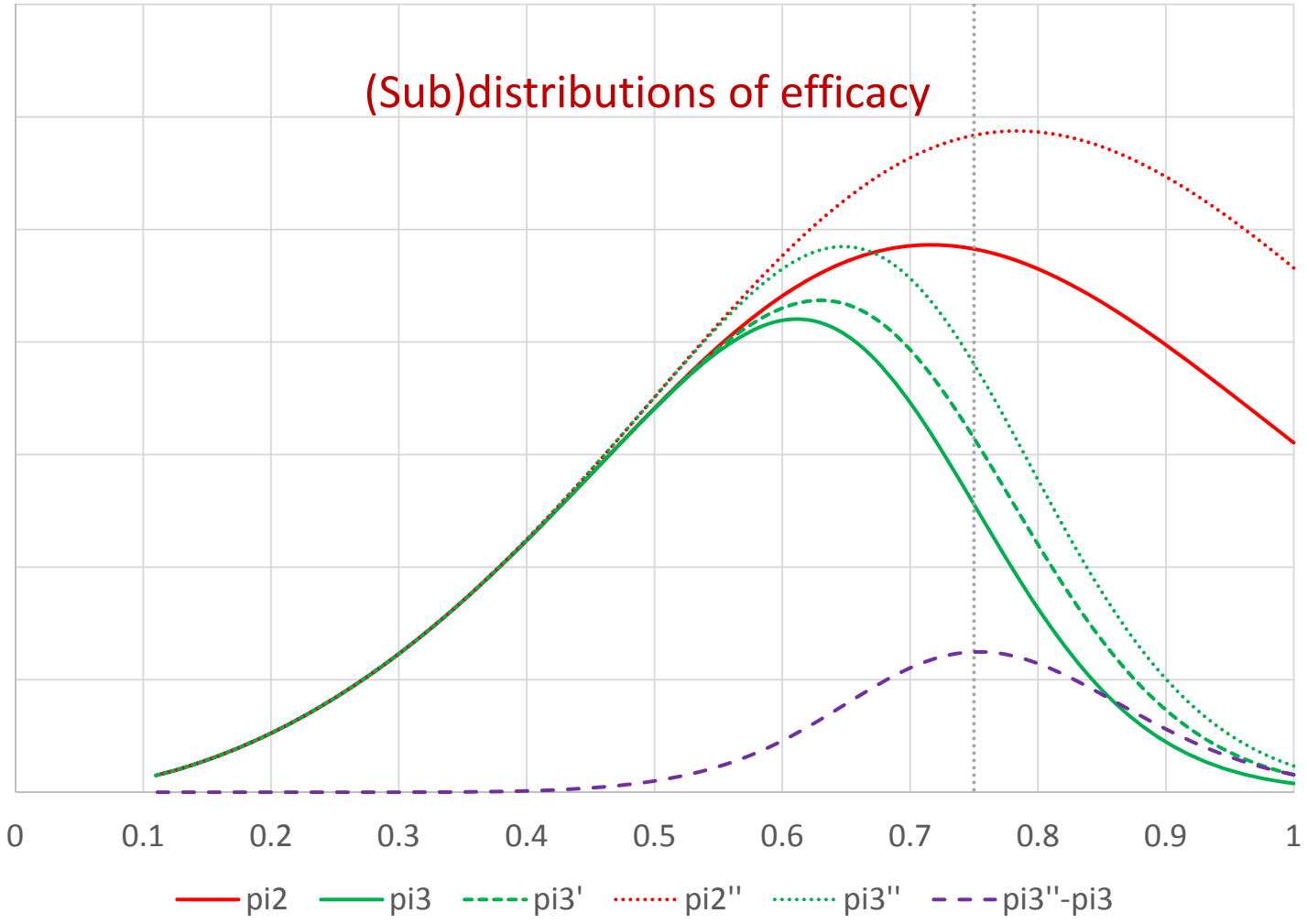
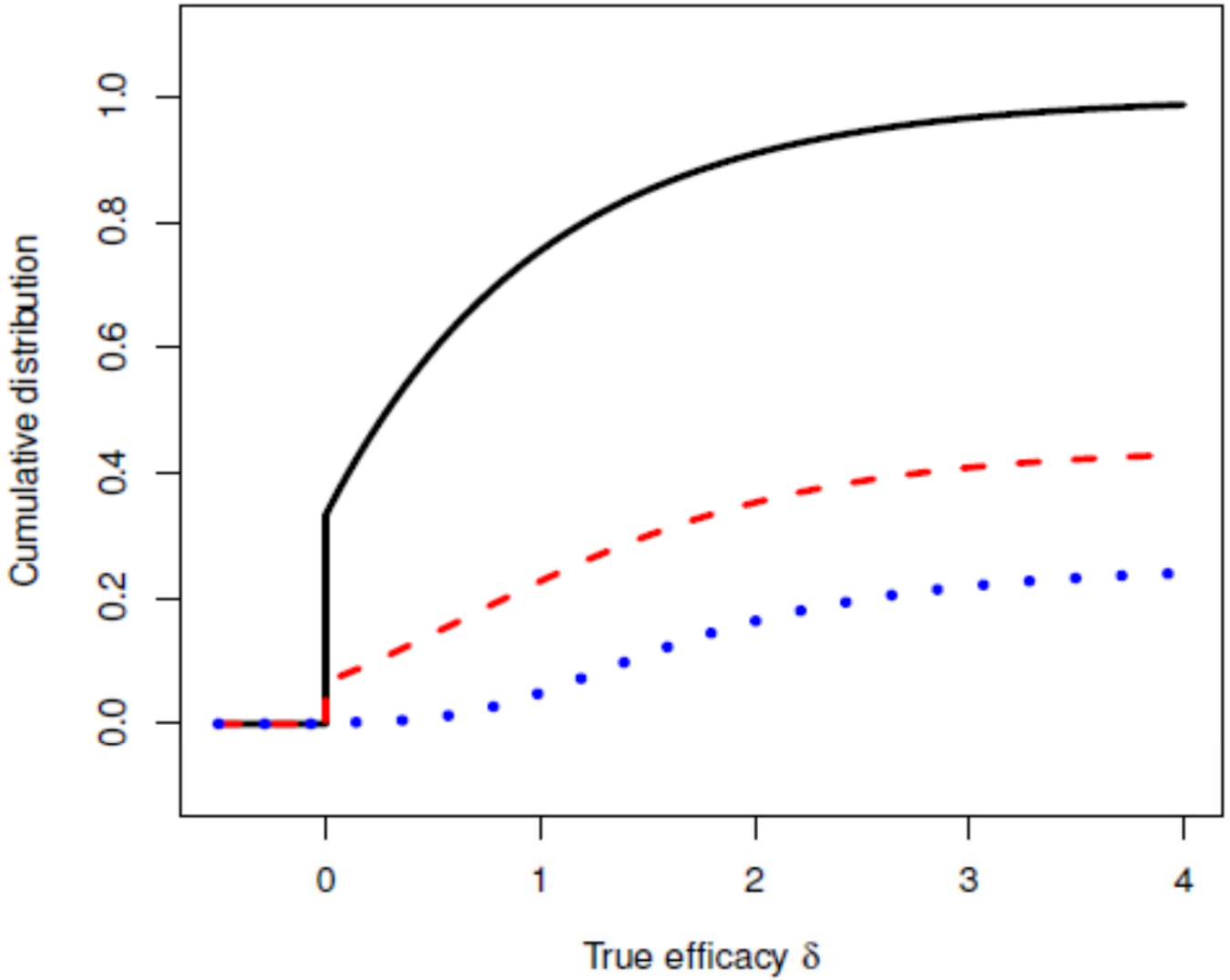
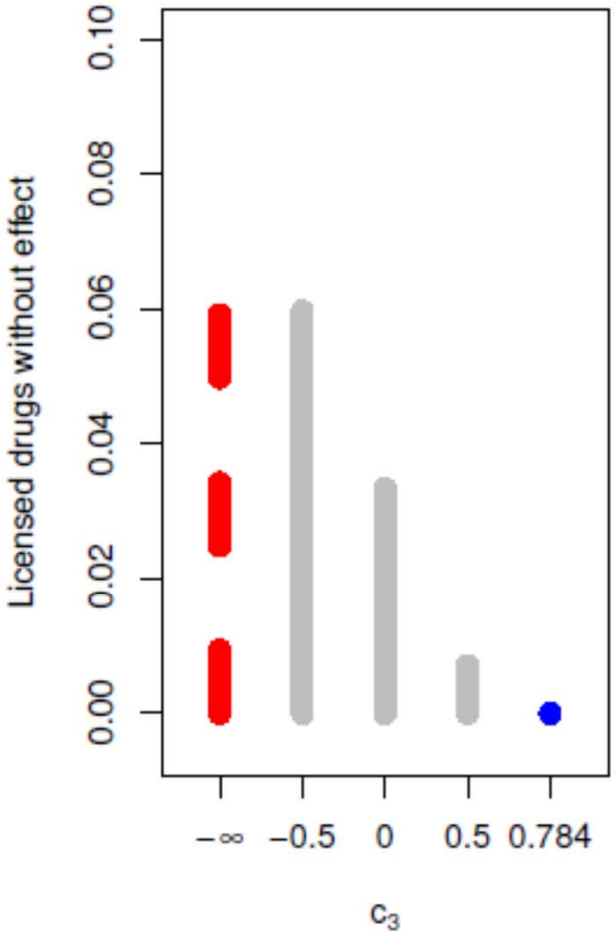

(Sub)distributions of efficacy
0
0.1
0.2
0.3
0.4
0.5
0.6
0.7
0.8
0.9
1
pi2
pi3
pi3'
pi2''
pi3''
pi3''-pi3

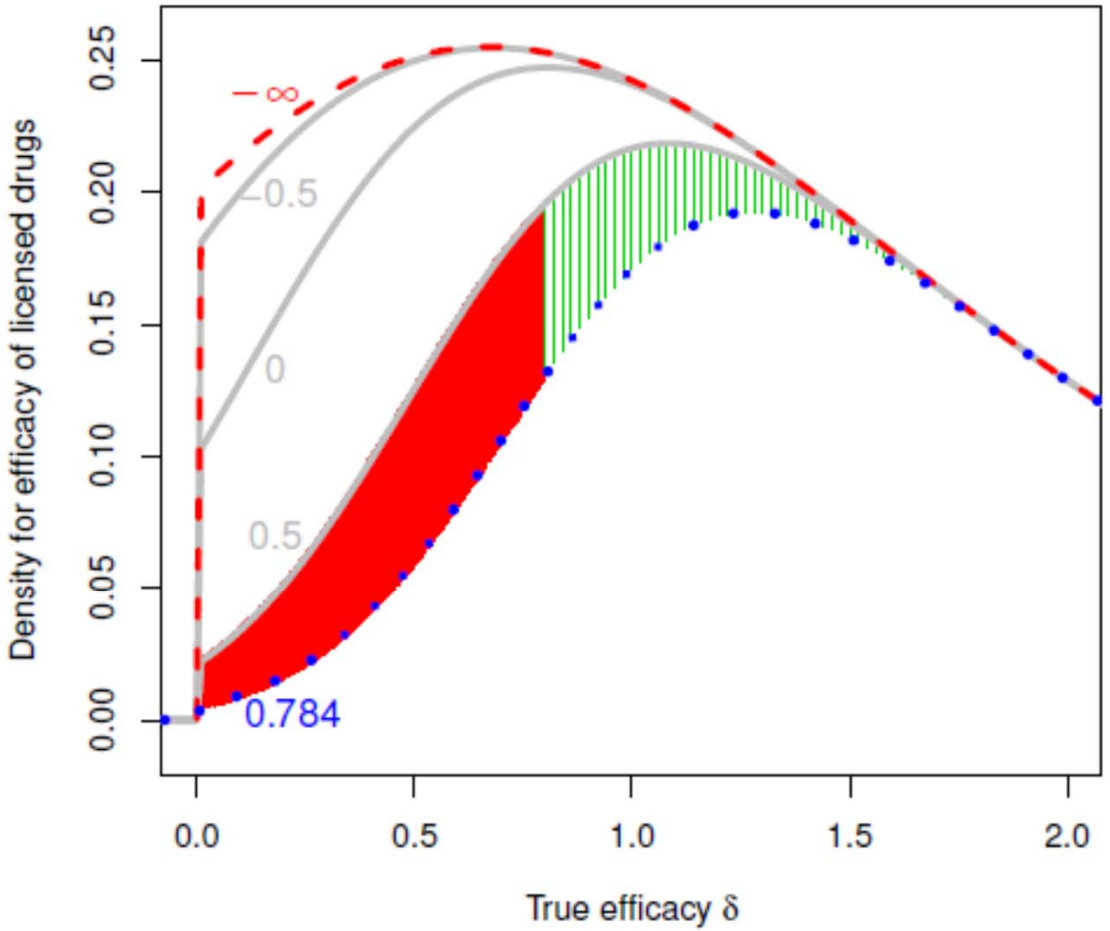
Table 1: Efficacy-distribution of drugs remaining during development process

Stage	Efficacy-distribution
Phase II	$\pi_1(\delta)$
Phase III	$\pi_2(\delta) = \int_{-\infty}^{\delta} \Phi((x - c_2)/\sigma_2)\pi_1(\partial x)$
Licensed	$\pi_3(\delta) = \int_{-\infty}^{\delta} \Phi((x - c_3)/\sigma_3) \cdot \Phi((x - c_2)/\sigma_2)\pi_1(\partial x)$

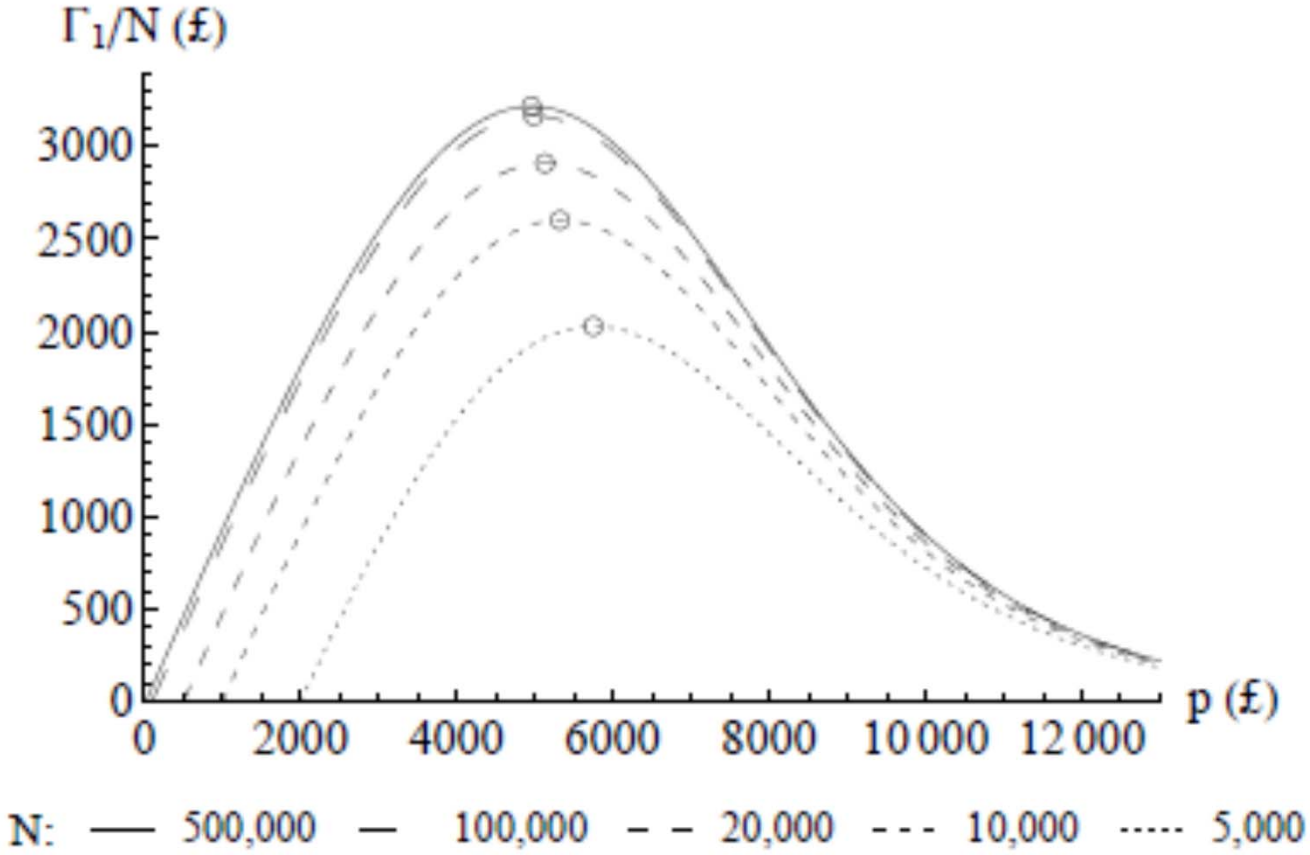
Distribution of drugs
Before and after Phase III and approved




Licensed drugs without effect
0.00
0.02
0.04
0.06
0.08
0.10
−∞
−0.5
0
0.5
0.784
c3


Density for efficacy of licensed drugs
0.00
0.05
0.10
0.15
0.20
0.25
−∞
−0.5
0
0.5
0.784
0.0
0.5
1.0
1.5
2.0
True efficacy δ

PRICING



(a) Stage 1 expected profit per patient to benefit, (Γ_1/N), as a function of the HTP's proposed Stage 1 price, p, for different values of N. Circles indicate maxima.

Conclusions

- ”Rational” sponsors base investment decisions on regulatory and payer rules
- Society (RA+payer) should take such incentives into account when optimizing regulatory requirements and willingness-to-pay
- In-transparency in RA/payer rules carry a cost for everyone
- Optimal designs when different subpopulations exist depends on factors such as efficacy prior and prevalence
- Optimal designs from a sponsor and societal perspective may differ substantially
- Everything else fixed, it is optimal for society to lower the regulatory requirements and pay more for orphan drugs

References

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- Burman. From optimal design theory to optimizing designs of clinical trials. *Festschrift in Honor of Hans Nyquist on the Occasion of His 65th Birthday.* Ed: Fackle-Fornius (2015).
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- Miller, Burman. A decision theoretical modeling for Phase III investments and drug licensing. *Submitted* (2016).
- Jobjörnsson. R-package BDPOPT, (2015).

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