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Quantitative Decision-Making in Drug Development

Gaëlle Saint-Hilary

PhD Student, Politecnico Di Torino (Italy) and Institut de Recherches Internationales Servier (France)

SFdS, Journée Nationale Biopharmacie & Santé

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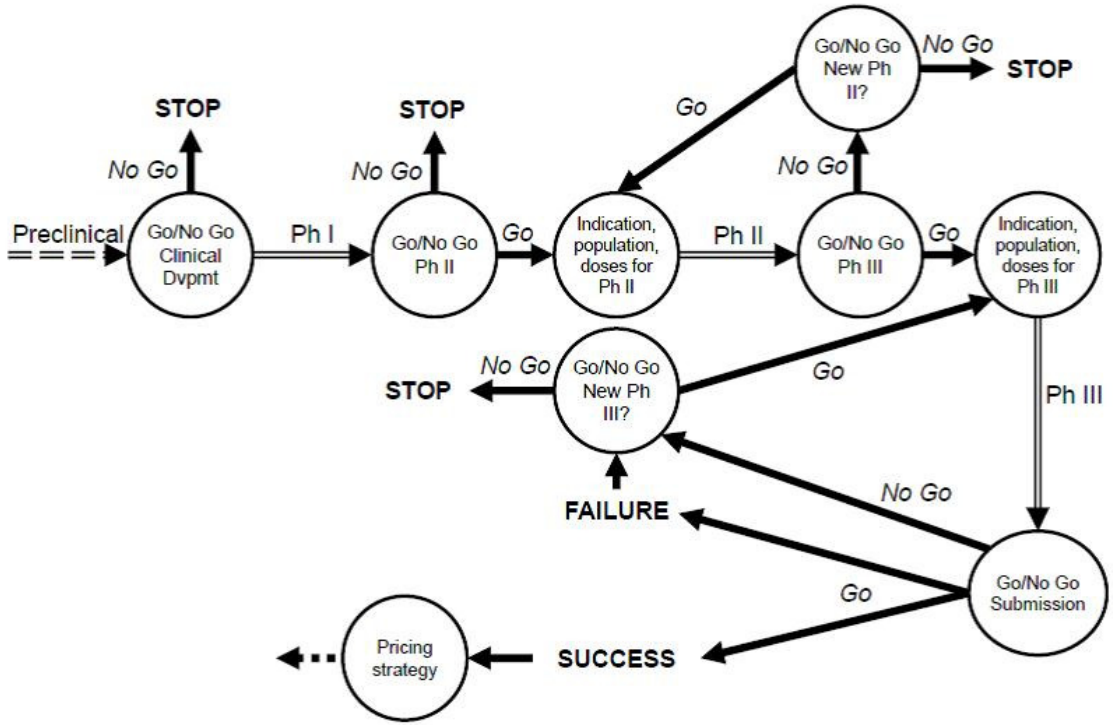
Outline

- Introduction
- Predictive Probability of Success
- Quantitative criteria for Go/No Go decisions
- Portfolio optimization
- Conclusion

Decision-making in drug development

Making an **optimal** choice between **several alternatives** based on the **available information** and **preferences of the decision maker**



Example of decision-making in clinical drug development

Decision-making in drug development Examples

- **Study level**
  - Dose selection
  - Population
  - Design (sample size, control arms, optimal duration and timing)
- **Development level**
  - Indication, population
  - Number of studies, timing of the studies
- **Portfolio level**
  - Drugs to develop
  - Budget allocation
  - Time allocation

How can we compare and optimize study designs, development plans and business strategies given budget and time constraints?

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Predictive Probability of Success Introduction

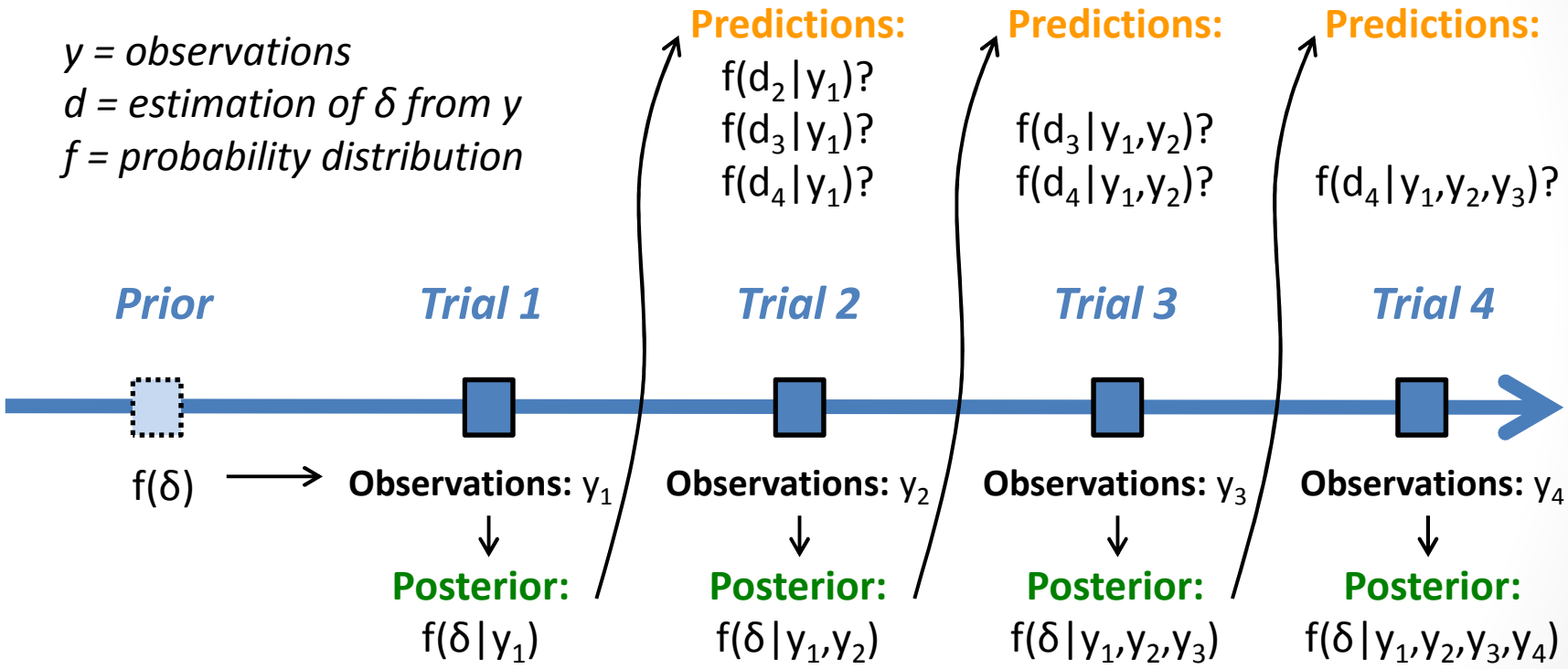
Given what has been observed already, what are the chances of success of the next trials?

- **Success** usually defined as a statistically significant result (Spiegelhalter 2004, O'Hagan 2005)
- **Predictive Probability of Success (PPS)** = weighted average power with greater weight given to more likely treatment effects (i.e. those close to the observed results in the past trials)
- Note: also used to support stop/continue decisions at interim analyses
  - See for example publications Gasparini (2013) and Tang (2015)

Predictive Probability of Success Methods

For one parameter δ (e.g. difference between treatment and control)

y = observations
d = estimation of δ from y
f = probability distribution



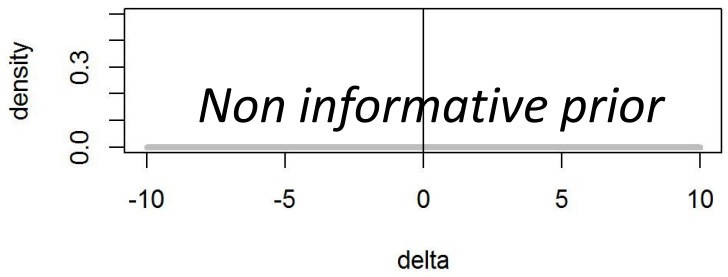
Success of trial i: $d_i > c$ c = critical value

$$PPS = P(d_i > c) = \int \int_{d_i > c} f(d_i \mid \delta)\, f(\delta \mid y_1, \ldots, y_{i-1}) d(d_i) d(\delta)$$

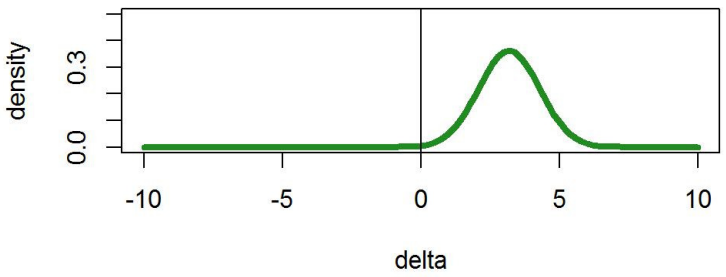
Predictive Probability of Success Example for a Normal distribution

After Study 1, Predictions for Study 2

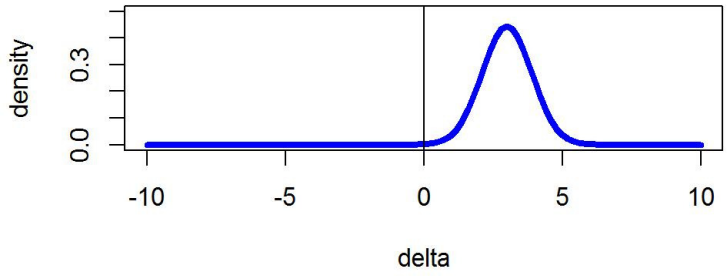
Prior: f(δ)



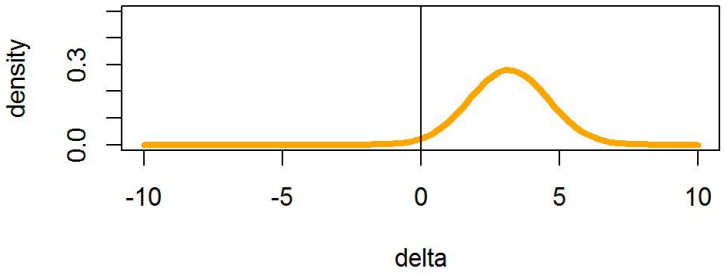
Posterior: $f(\delta | y_1)$



$f(d_2 | \delta=3)$

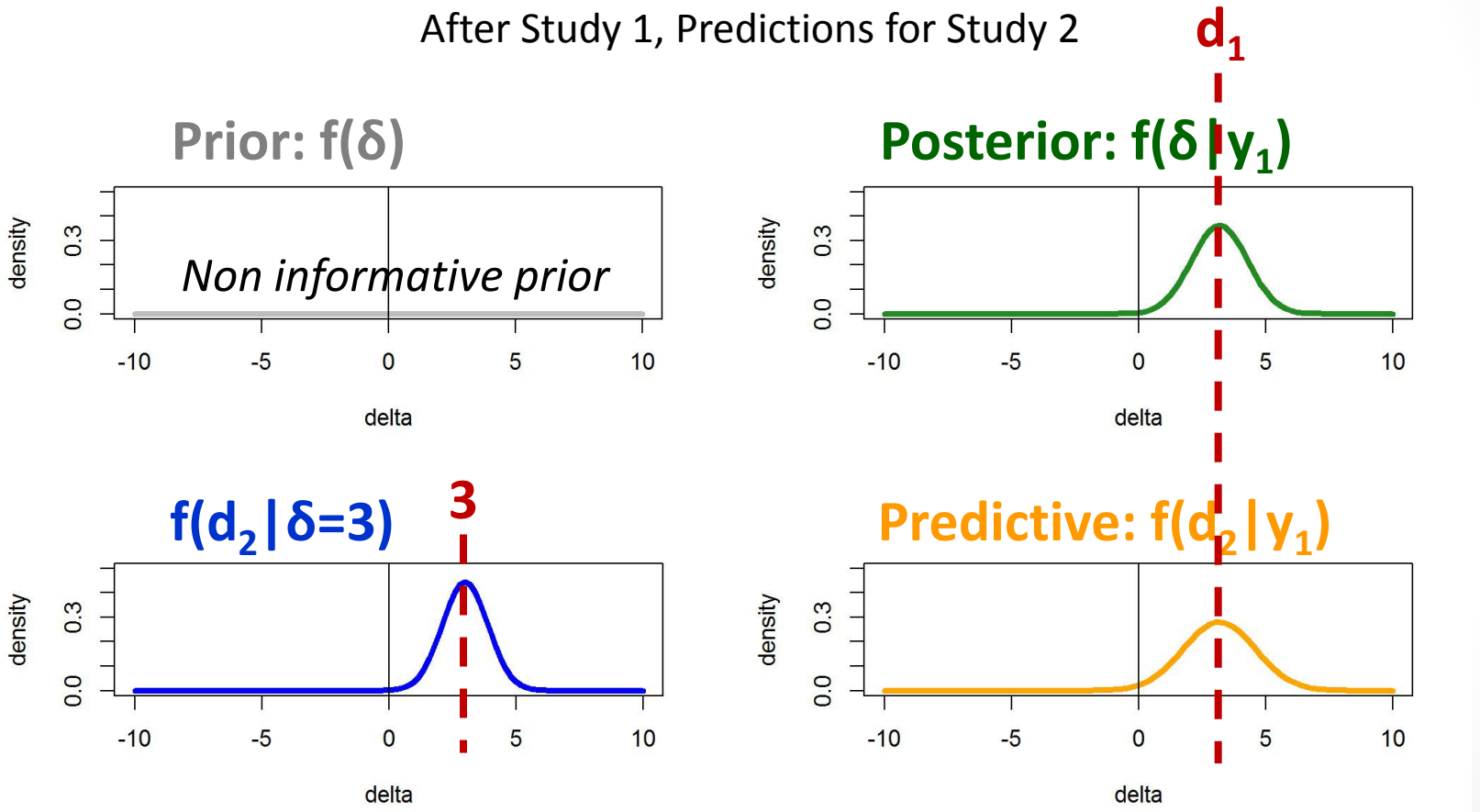


Predictive: $f(d_2 | y_1)$



Var (predictive) = Var ($f(d_2 | \delta=x)$) + Var (posterior)

Predictive Probability of Success Example for a Normal distribution



Predictive Probability of Success Example for a Normal distribution

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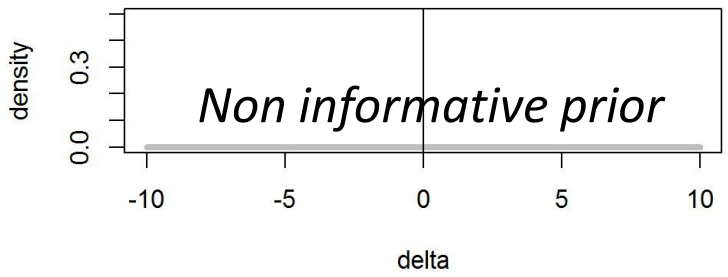
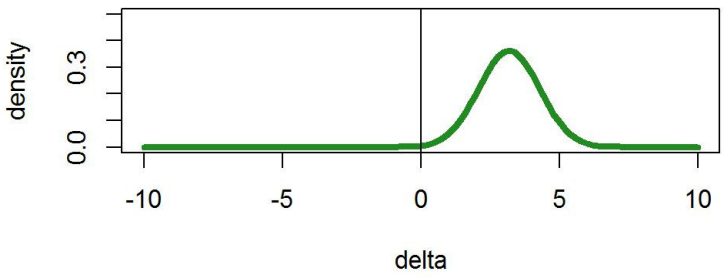
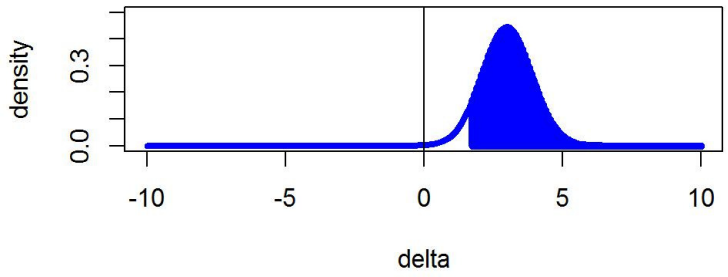


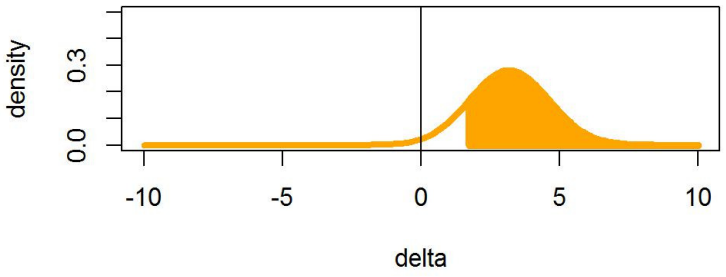
Posterior: $f(\delta|y_1)$



$f(d_2|\delta=3)$



Predictive: $f(d_2|y_1)$



Power = 92%

Predictive probability of success*= 84%

* Success = statistically significant result

Predictive Probability of Success Example

Compare 3 different development strategies

- S1-S2-S3 : 1 'preliminary Phase 3' trial + 1 full Phase 3 study
- S1 and S2 : conduct these trials with 2 different doses
- S3 : 1 dose determined by a 'Phase 2b trial'
- Success = significant result in a test of superiority and satisfying a safety condition

	S1	S2	S3
Outcome Assurances			
Failure at Phase 2b	0.000	0.000	0.145
Failure at preliminary Phase 3	0.056	0.068	0.023
Failure for futility at futility analysis	0.050	0.102	0.034
Failure for safety at interim analysis	0.049	0.021	0.044
Failure for futility at interim analysis	0.039	0.076	0.025
Success at interim analysis	0.253	0.267	0.226
Failure for efficacy at final analysis	0.063	0.102	0.052
Failure for safety at final analysis	0.128	0.068	0.118
Success at final analysis	0.362	0.296	0.333
FAILURE	*0.385*	*0.437*	*0.441*
SUCCESS	*0.615*	*0.563*	*0.559*

Table 1. Assurances for three different strategies.

Source: O'Hagan 2005

Predictive Probability of Success Conclusion

- The **definition of "success"** should be agreed with the project team
- **Evidence-based** methods
  - Based on prior knowledge rather than on questionable hypotheses
  - Clinical data should be available: may not be appropriate in very early development
  - Bayesian framework: PPS are updated with the accumulation of knowledge from trial to trial
- What is a **"good PPS"**?
  - Phase/disease/project/team dependent
  - Low amount of evidence → PPS close to 50% → Uncertainty to take a decision
- Previous and future trials should be done in the **same context**
  - Endpoint, regimen, duration, population…
  - Otherwise, the relationship between the parameters of the different contexts should be considered

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- Introduction
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- **Quantitative criteria for Go/No Go decisions**
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Quantitative criteria for Go/No Go decisions Introduction

MAIN PAPER

Pharmaceutical Statistics

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Decision-making in early clinical drug development

Paul Frewer,[a]* Pat Mitchell,[a] Claire Watkins,[b] and James Matcham[a]

- Inspired from Lalonde 2007

- **Systematic approach requested by the governance boards in AstraZeneca Early Clinical Development**

Quantitative criteria for Go/No Go decisions Decision framework (Frewer 2016)

- Three outcome decision

- Decision parameters

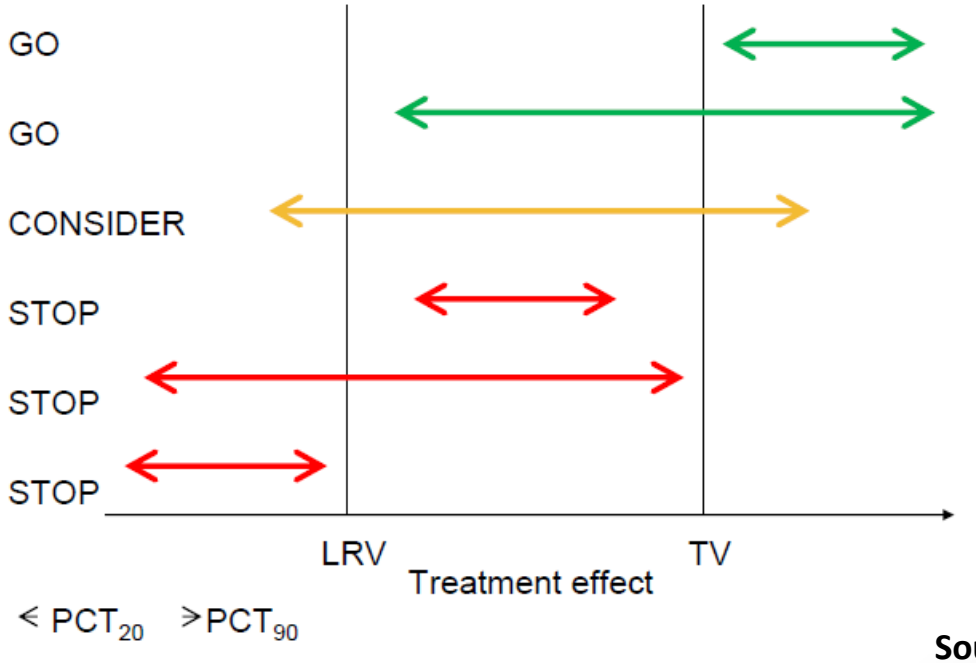
Target Value (TV)	Desired level of performance
Lower Reference Value (LRV)	Minimal level of performance
False Stop Risk	Risk of a “Stop” decision if the truth is better than the TV (typically10%)
False Go Risk	Risk of “Go” decision if the truth is at worse than the LRV (typically 20%)

Quantitative criteria for Go/No Go decisions Visualization of the framework (Frewer 2016)

- **Go** if : PCT_{20}> LRV and PCT_{90}> TV
- **Consider** if : PCT_{20}≤ LRV and PCT_{90}> TV
- **Stop** if : PCT_{90}≤ TV

Where PCT_x denotes the *x*-th percentile of the distribution of the estimated treatment effect

- **All possible cases:**

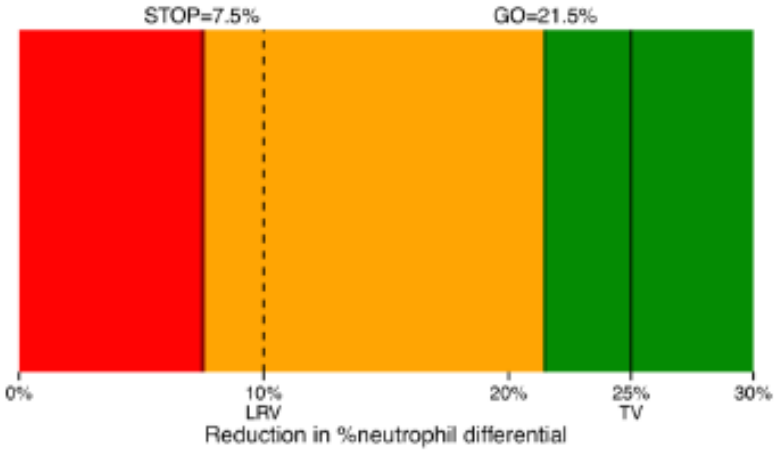


Source: Frewer 2016

Quantitative criteria for Go/No Go decisions Example

Go/No Go criteria for neutrophil differential used as a **biomarker** for Chronic Obstructive Pulmonary Disease (COPD)

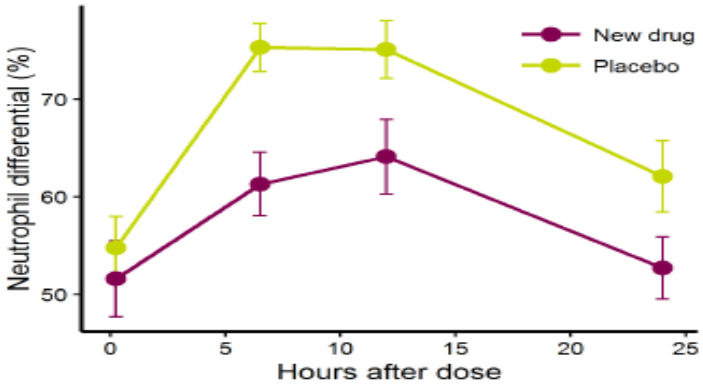
1) Decision framework



2) Operating characteristics

	Probability of different decisions under different true effects				
True effect (reduction)	Go	Indecisive	Stop	Go or Indecisive	Stop or Indecisive
TV (25%)	60%	30%	10%	90%	40%
LRV (10%)	20%	38%	42%	58%	80%
Placebo (0%)	6%	25%	69%	31%	94%

3) Results: the observed level of reduction turned out to be 56%: indicates a clear **GO**



Source: Taib 2016

Quantitative criteria for Go/No Go decisions Discussion (Frewer 2016)

- The chance of being in the "Consider" zone should not be too high → importance of **operating characteristics**
- **Consistent approach** to quantitative decision making for **all** phase decisions
  - Early phases: decision criteria can be based on biomarkers
  - Late phases: decision criteria can be based on PPS
- **Univariate** approach, could be extended to multiple endpoints
  - For 2 endpoints: 9 different scenarios → the clarity of the decision process decreases with the number of endpoints
- **Clear, simple** approach
  - Governance boards are enthusiastic with the "traffic-light framework"
  - Concerns are raised by statisticians : too much focus on the result, lack of understanding of the method and its uncertainties

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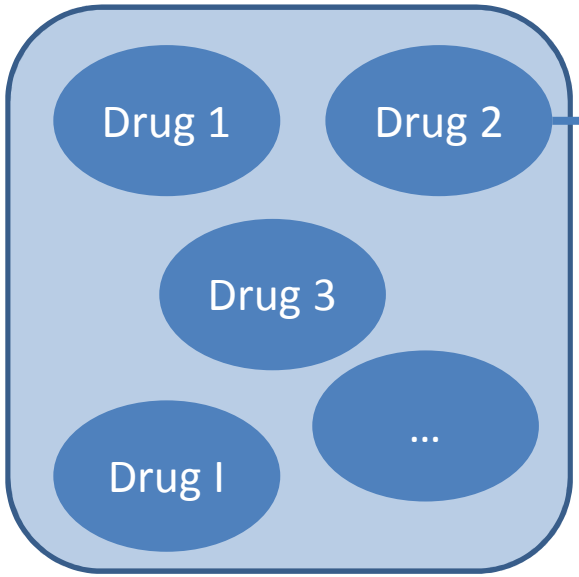
Portfolio optimization Introduction (Patel 2013)

PORTFOLIO

Planning horizon: K months

Total budget: B_K



Drug i

For 2 future trials

Drug effect assumptions

Mean response, SD of the response…

Designs assumptions

j=1,…,J set of possible trial designs

n_{ij} = sample size for design j for drug i

Cash flow assumptions

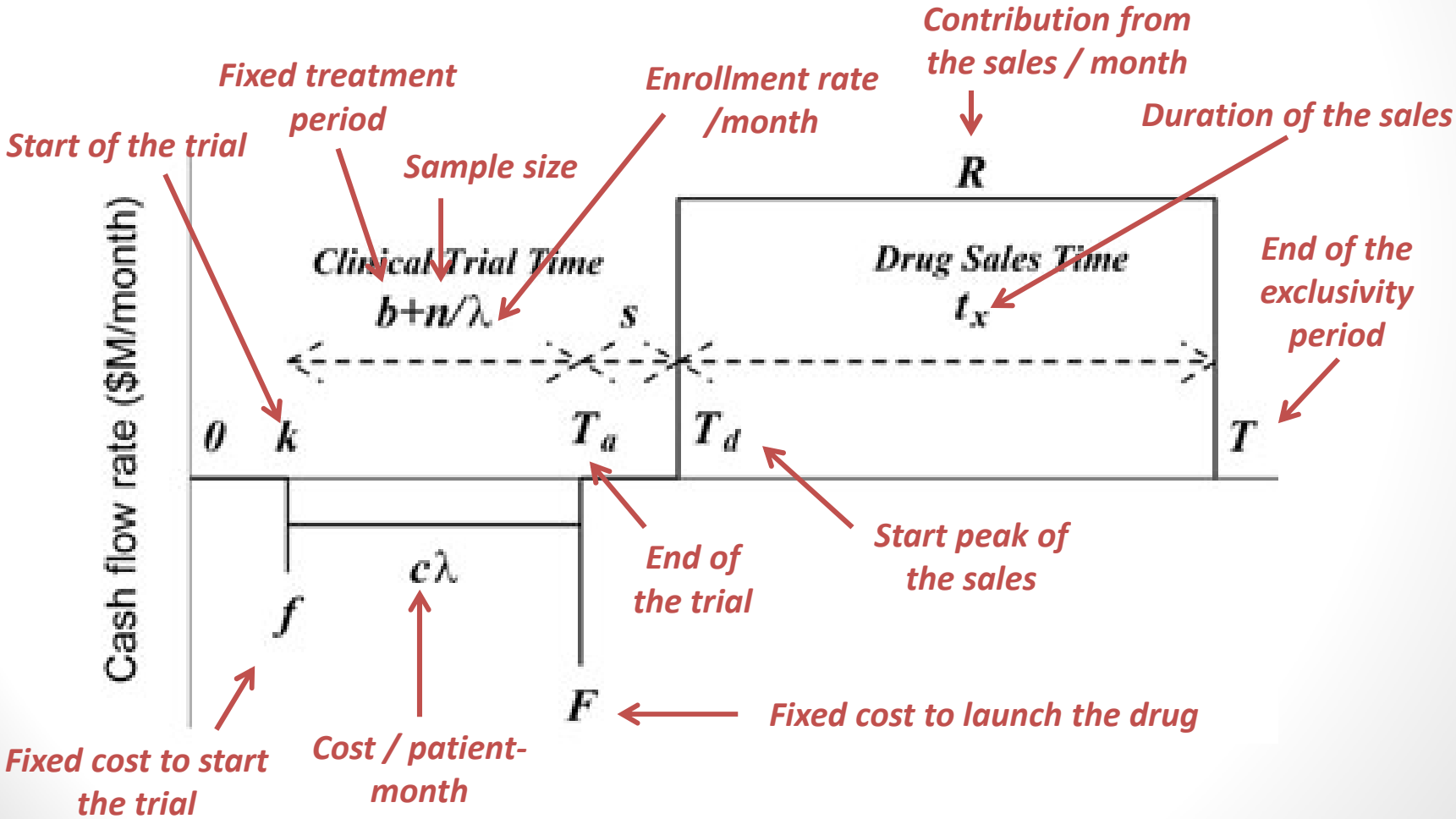
k=1,…,K month of the start of the trials

(other parameters, see next slide)

Objective: find the optimal sample size n_{ij} and the optimal month k of start of the trials for each drug in order to **maximize the expected financial value of the portfolio**

Portfolio optimization Introduction (Patel 2013)

- **Cash flow assumptions: lot of assumptions**



Source: Patel 2013

Portfolio optimization Methods (Patel 2013)

- **Expected Net Present Value** for drug i with trial design j started at month k

$$ENPV_{ijk} = PPS_{ij}.NPV_{ijk}|Go + (1 - PPS_{ij}).NPV_{ijk}|NoGo$$

  - Based on the **drug effect assumptions** and the **design assumptions** we can calculate the **PPS_{ij}** = Predictive Probability of Success
  - Based on the the **design assumptions** and the **cash flow assumptions** we can calculate the Net Present Values:
    - **$NPV_{ijk}|Go$** = Revenue from the sales – Cost of the trials
    - **$NPV_{ijk}|NoGo$** = 0 – Cost of the trials

- **Objective : maximize the total ENPV according to the size of the trials n_{ij} and the month k of the start of the trials**

$$ENPV_{Total} = \sum_i \sum_j \sum_k ENPV_{ijk}$$

for trials started at time k

Portfolio optimization Results (Patel 2013)

Drugs in the portfolio

Table I. Financial, scheduling, and Bayesian prior parameters and optimum solution.

	Drug 1	Drug 2	Drug 3	Drug 4	Drug 5	Drug 6	Drug 7
Parameters							
Mean response (δ_i)	0.5	0.4	0.5	0.4	0.4	0.3	0.25
SD of response (σ_i)	2	1.8	2	2	1.5	1.5	1
1st in class?	No	Yes	No	No	Yes	Yes	Yes
SD of Bayesian prior for placebo (ψ_i^0)	0.15	0.15	0.15	0.15	0.15	0.05	0.15
SD of Bayesian prior for drug (ψ_i)	0.15	0.3	0.15	0.15	0.3	0.2	0.3
Trial fixed cost (f_i, K$)	2805	15	525	2125	240	125	500
Patient cost (c_i, K$)	11	17	25	24	26	15	14
Fixed setup cost (F_i, m$)	50	500	400	300	500	300	1000
Contribution (R_i, m$/month)	175	85	400	200	45	250	500
Market size	M	S	L	M	S	M	L
Exclusivity period (T_i, months)	108	120	135	180	155	180	145
Month when drug will be available for phase 3 trials	1	1	3	6	13	18	25
Enrollment rate (λ_i, patients/month)	30	50	40	60	60	50	45
Treatment period per patient (b_i, months)	0.3	1	12	12	24	6	12
Optimal solution							
Optimal solution							
Optimal sample size	832	1054	832	1300	732	1300	674
Optimal ENPV (m$)	4818	1849	10057	5643	457	5959	5754
Optimal schedule (month)	1	1	3	6	13	18	25
Probability of success (PoS_{ij})	0.67	0.49	0.67	0.60	0.49	0.53	0.38

ENPV, expected value of net present value; SD, standard deviation; S, small; M, medium; L, large.

Drug effect

Budget

Time

Source: Patel 2013

Portfolio optimization Discussion (Patel 2013)

- Maximizes the **value of a portfolio** under a **global budget constraint**
  - Better than optimizing each drug separately
  - Optimizes the variables that have the greatest impact on the costs: sample size and timing
- **Complexity**
  - Lot of assumptions: high level of uncertainty → importance of sensitivity analyses
  - Challenging communication with governance boards
- Focus on the **financial** value of the portfolio
  - Lack of clinical considerations? → optimal solution between clinically and scientifically justified proposals
- Integration of knowledge of experts with different specializations (statistics, finance, strategy, regulatory affairs…)

General Conclusion

- **Quantitative Decision-Making is increasingly used in the Pharmaceutical Industry**
- There is not one general and comprehensive method
- **Evidence-based** methods avoid relying on questionable assumptions
- **Subjectivity** (preferences, targets) can be incorporated but should be challenged
- Increased **complexity** → more comprehensive methods but increased **uncertainty** and **challenging communication**
- Importance of sensitivity analyses
- **Implementation**: decision tools are developed/in development

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