EUROPEAN FEDERATION OF STATISTICIANS IN THE PHARMACEUTICAL INDUSTRY
Representing Statistical Associations in Europe

EFSPI SIG Quantitative Decision Making
Experience sharing

Gaëlle Saint-Hilary

Co-chair of the SIG

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EFSPI Statistics Leaders meeting, 12 July 2018

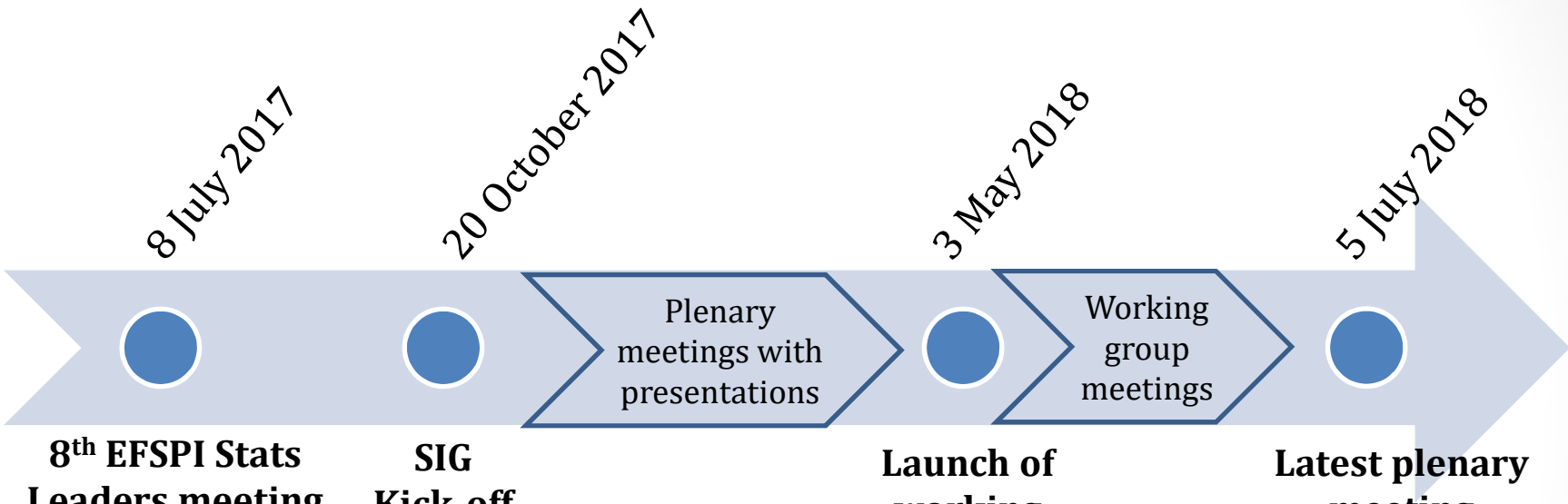
POLITECNICO DI TORINO
Dipartimento di Scienze Matematiche

SERVIER

Outline

- Background, members, objectives
- Examples from the industry: quick overview
- Working groups
- 1-day EFSPI meeting
- Collaboration with the SIG Benefit-Risk
- Operational aspects
- Conclusion

Background



8th EFSPI Stats Leaders meeting
Proposal of a SIG Quantitative Decision-Making by Maylis Coste (Servier) and Sylvain Nicolas (Sanofi)

SIG Kick-off meeting

Launch of working groups

Latest plenary meeting
18 members from 14 companies / universities

SIG: Special Interest Group

Members

(as of July 2018)

- Juan Abellan (GSK)
- Gianluca Baio (UCL)
- Nicolas Bonnet (Sanofi)
- Sarah Bray (Amgen)
- Alex Carlton (GSK)
- **Pierre Colin, co-chair (Sanofi)**
- Maylis Coste (Servier)
- Cecile Dubois (Grunenthal)
- Beki Finch (Roche)
- Paul Frewer (AstraZeneca)
- Heiko Götte (Merck)
- Martin Johnson (UCB Pharma)
- John-Philip Lawo (CSL Behring)
- Emmanuel Pham (Ipsen)
- Laurent Quinquis (Danone)
- Veronique Robert (Servier)
- **Gaëlle Saint-Hilary, co-chair (Politecnico di Torino)**
- Guido Thömmes (Grunenthal)

Objectives of the SIG

- To **share** (anonymized) **cases studies** of how quantitative decision-making methods have been used within pharmaceutical companies
- To perform **literature reviews**, discuss and make **recommendations** on existing methodologies in terms of approach and interpretation
- To **develop new methodologies** or practices where needed
- To **promote the role of the statistician** in supporting decision-making in pharmaceutical companies and/or other stakeholders
- To **propose trainings, public meetings or publications** to share methods and experience

Examples from Grünenthal

Use of assurance in the design of a trial

Primary endpoints

Endpoint	Test	Assurance (%)
Primary (EP1)	Superiority vs Placebo	93.0
Co-primary (EP2)	Superiority vs Placebo	89.3

Secondary endpoints

Endpoint	Test	Assurance (%)
Efficacy EP3	Superiority vs Placebo	68.8
Efficacy EP4	Superiority vs Placebo	21.8
Safety EP5	Superiority vs Comparator	92.8
Safety EP6	Superiority vs comparator	77.9

GRÜNENTHAL

Guido Thömmes

Bayesian decision framework for a PoC trial

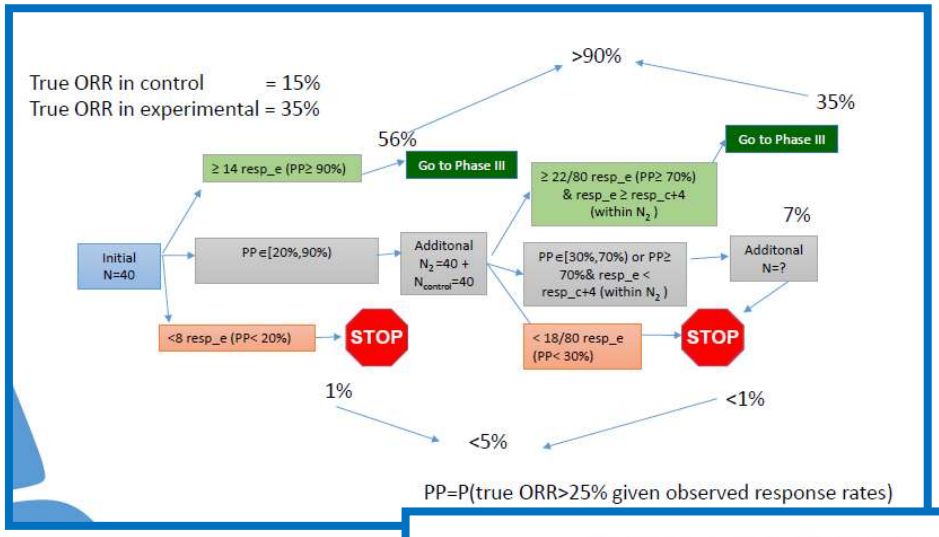
- Bayesian approach proposed by Fisch et al (2014)[a]
- The **dual criteria** will be formulated by means of posterior probabilities

  Significance: $Prob\{Effect > 0|Data\} > 1 - \alpha$

  Relevance: $Prob\{Effect > TD|Data\} > 1 - \gamma.$
- The decisions are

	Significance	
Relevance	Yes	No
Yes	Go	Consider
No	Consider	NoGo

Examples from Merck

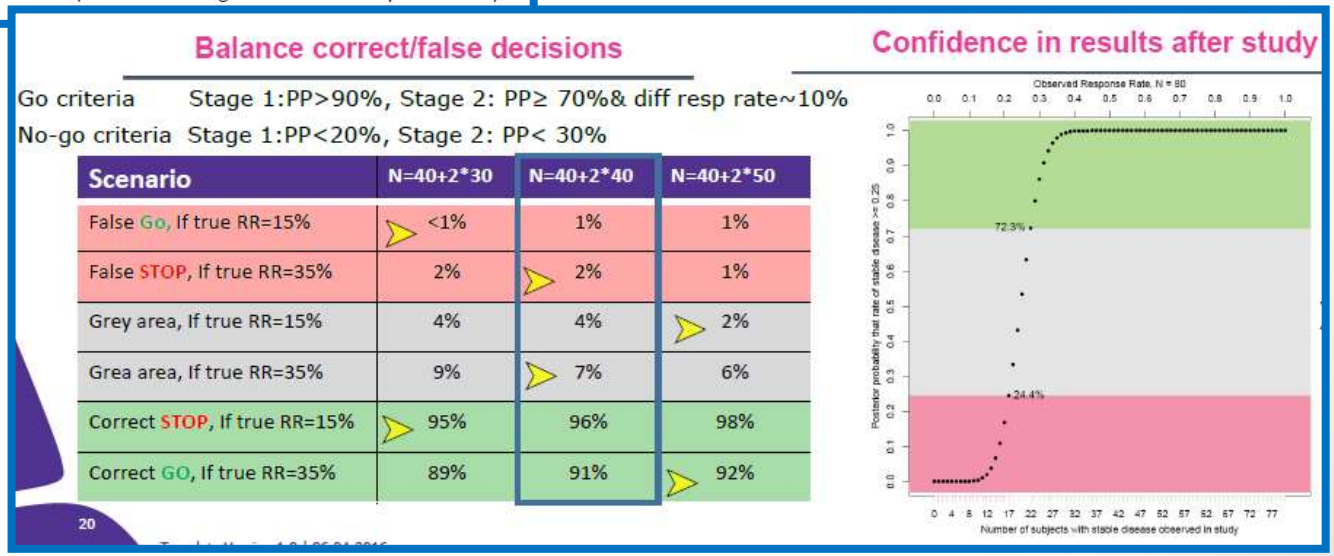


MERCK

Heiko Götte

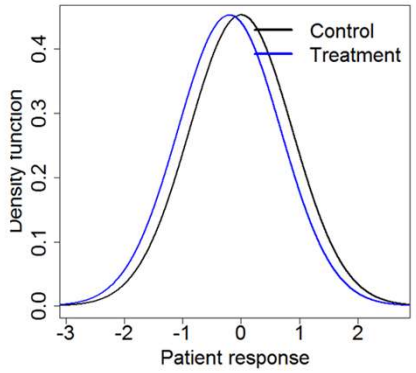
Decision-making framework based on the PoS

PoS: Probability of Success



Examples from Sanofi

- Model
  - $X_1 \sim N(\mu_1, \sigma_1^2)$, with $n_1 = 284$
  - $X_2 \sim N(\mu_2, \sigma_2^2)$, with $n_2 = 284$
- Information (based on 350+350 previous patients)
  - $\mu_1 \sim \mathrm{N}(0, 0.05^2)$
  - $\mu_2 \sim N(-0.2, 0.05^2)$
  - σ_1^2 and σ_1^2 distributions are obtained through the Cochran theorem (inverse-χ^2)
- Prediction
  - Test for non-inferiority
  - PoS = 0.91 (Monte Carlo approx.)



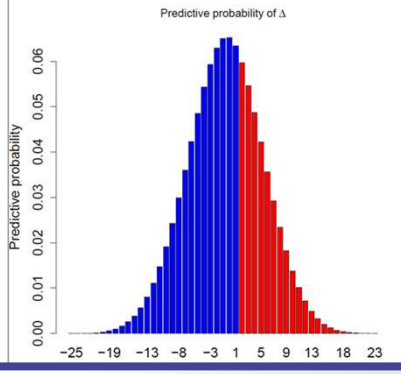
SANOFI

Pierre Colin

Case studies of PoS

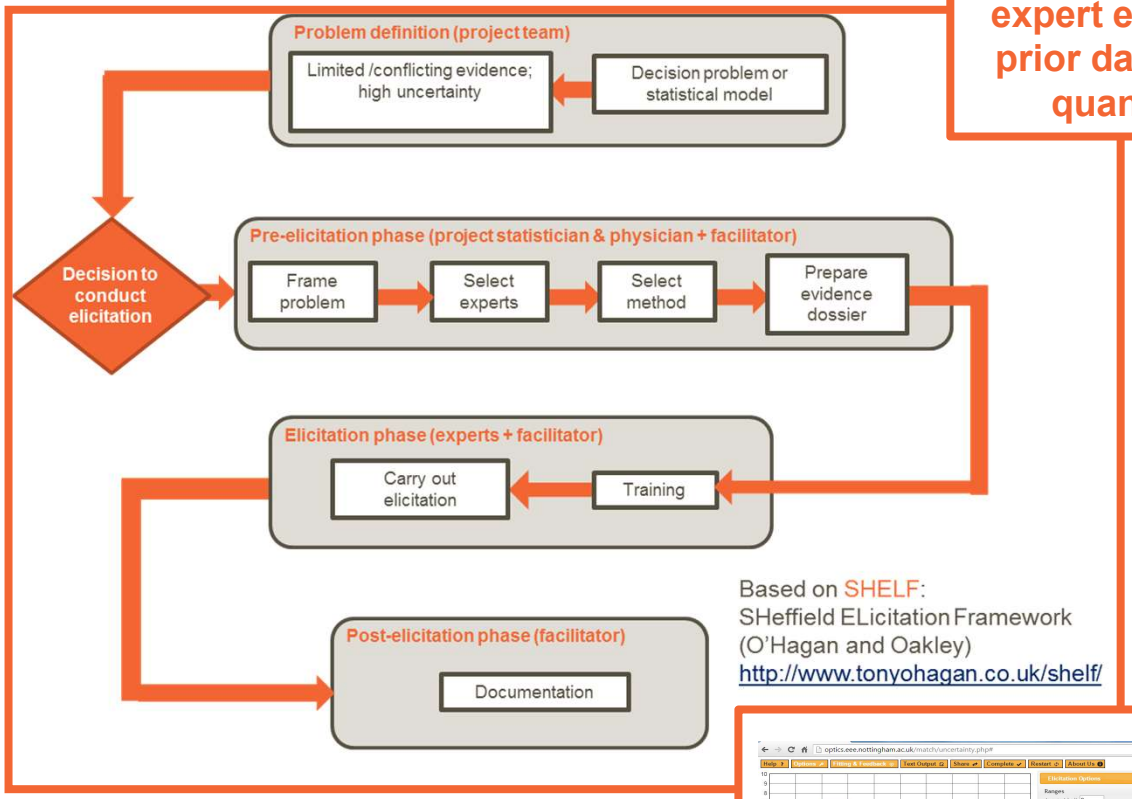
PoS: Probability of Success

- Prior distributions
  - $p_1 \sim Beta(10 \times 0.3, 10 \times 0.7)$
  - $p_2 \sim Beta(10 \times 0.3, 10 \times 0.7)$
- Criterion to predict
  - $\mathbb{P}(\Delta \geq 2 | N_1, \pi_1, N_2, \pi_2)$
- Predictive probability = 0.356

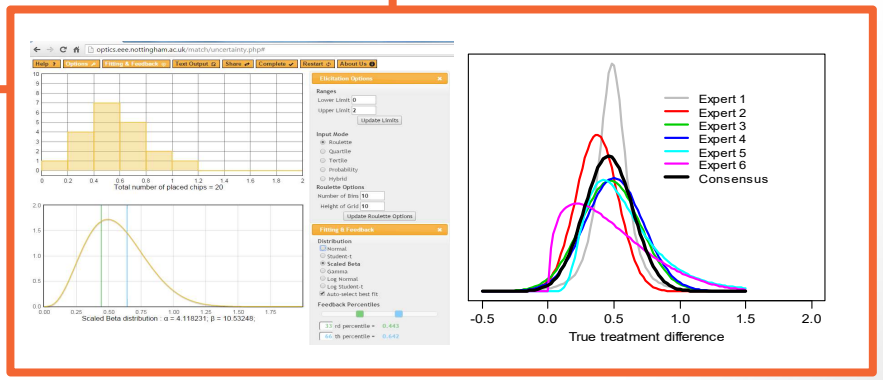


Examples from GSK

In 2014, GSK implemented a formal expert elicitation process to translate prior data and expert knowledge into quantitative prior distributions



Based on SHELF:
SHeffield ELicitation Framework
(O'Hagan and Oakley)
http://www.tonyohagan.co.uk/shelf/



SHELF: framework for prior elicitation

Juan Abellan

Examples from AstraZeneca

Three outcome decision

Go	Consider	Stop

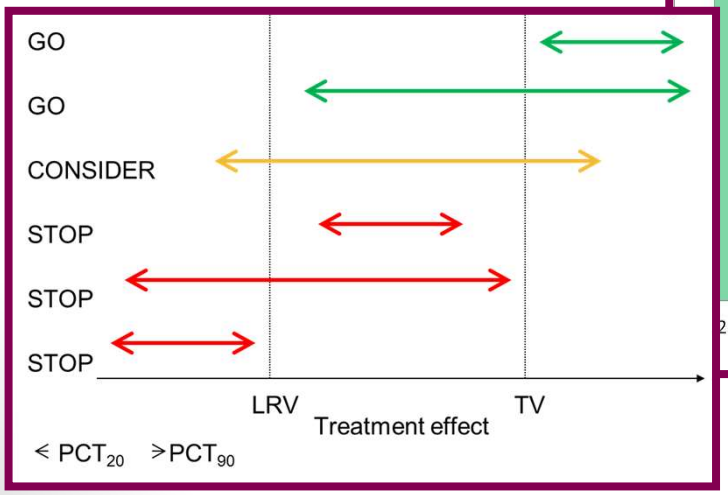
Decision parameters

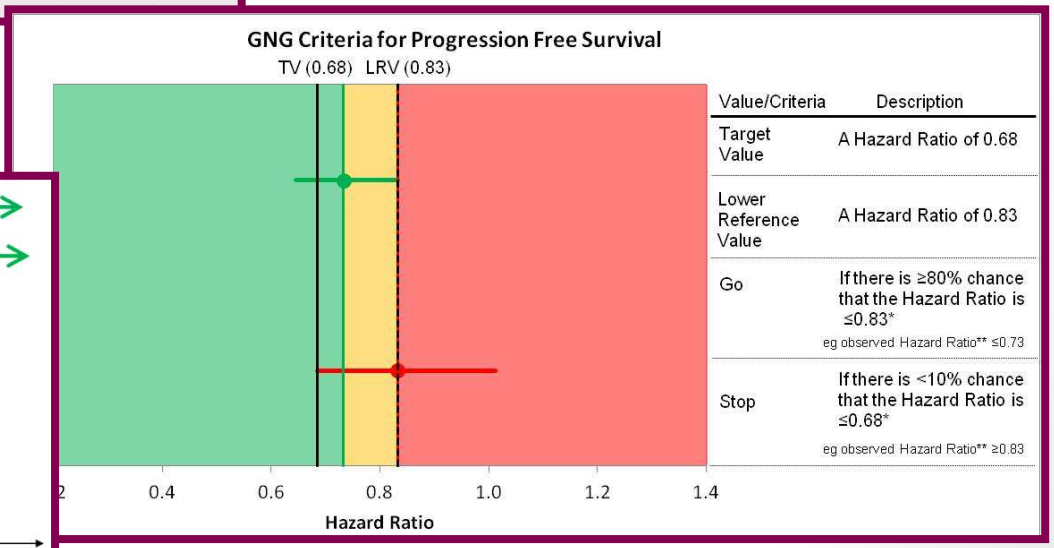
Target Value (TV)	Desired level of performance
Lower Reference Value (LRV)	Minimal level of performance
False Stop Risk	Risk of a "Stop" decision if the truth is better than the TV (typically 10%)
False Go Risk	Risk of "Go" decision if the truth is at worse than the LRV (typically 20%)

AstraZeneca

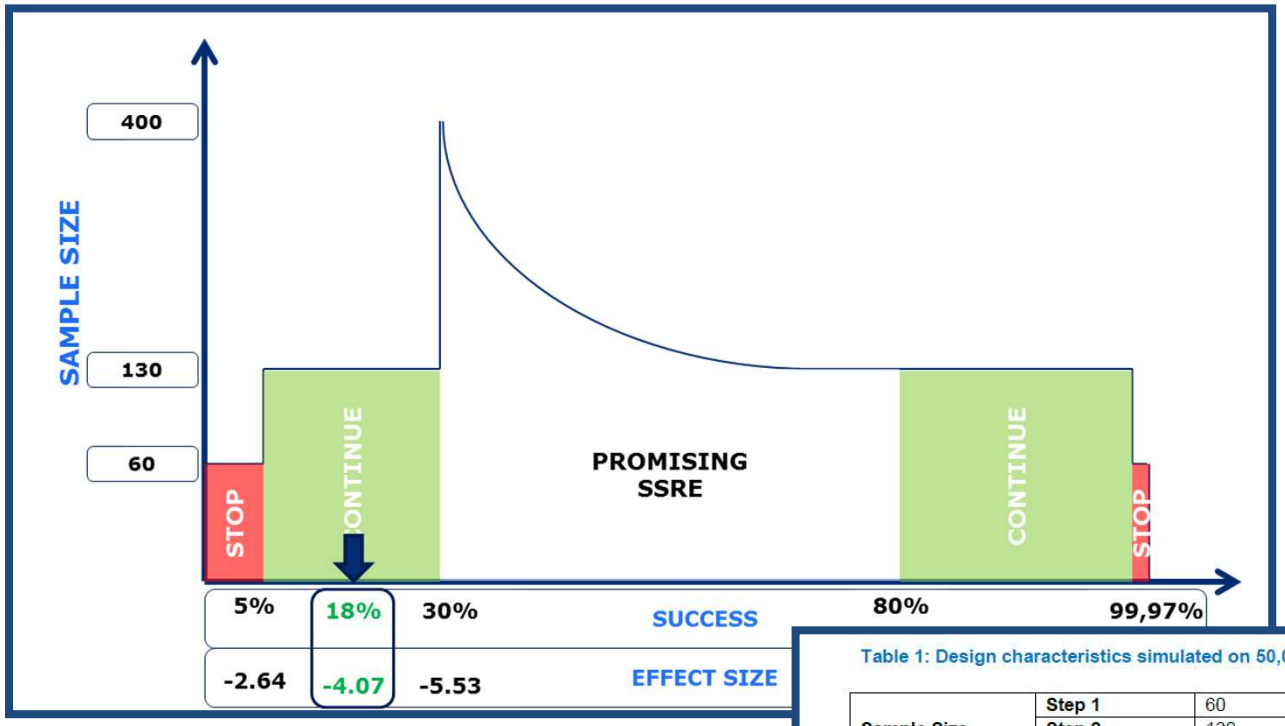
Paul Frewer

Decision-making framework (OKGO)





Examples from Danone



DANONE

Laurent Quinquis

Decision-making framework at interim analyses

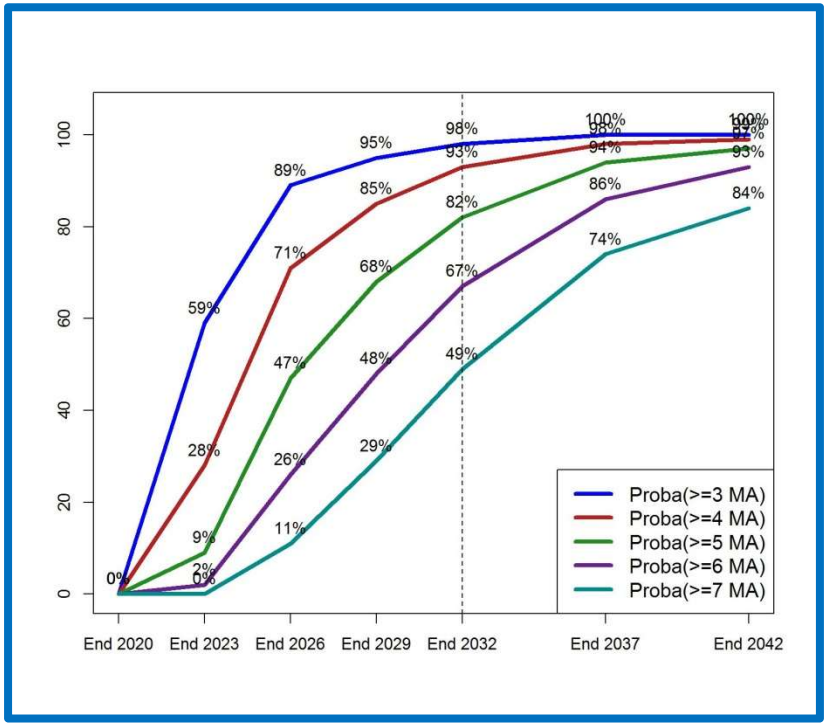
Table 1: Design characteristics simulated on 50,000 trials

Sample Size	Step 1	60						
	Step 2	130						
	Nmax	400						
Interim Analysis Thresholds: CP/p-value (Observed Effect)	CP for futility	≤5% (2.64)						
	Lower CP for SSRE	30% (5.53)						
	Upper CP for SSRE	80% (9.04)						
	CP for efficacy	99.97% (15.95)						
P-value at final		0.025						
Hypothesis*		Expected Overall Sample Size E(N)	Pr(Positive trial) CHW	Pr(Positive trial) Mehta & Pocock	Pr (IncrN)	Pr(Futile)	Pr (No change)	Pr (Eff Stop)
	H_1	136.1	86.01%	86.29%	23.0%	7.7%	56.9%	12.4%
	H_0	93.1	0.81%	1.05%	10.2%	69.4%	20.3%	0.1%

**50,000 Trial Simulations with a total planned Sample Size of 130 Subjects and an Interim at 60 Subjects, Assuming a Common SD=20; Simulations performed under H0: True Difference in Means = 0 and H1: True Difference in Means = 10 are displayed in the above Table.*

Examples from Servier

Predictions of the number of Marketing Authorizations over time



Decision-making at the portfolio level

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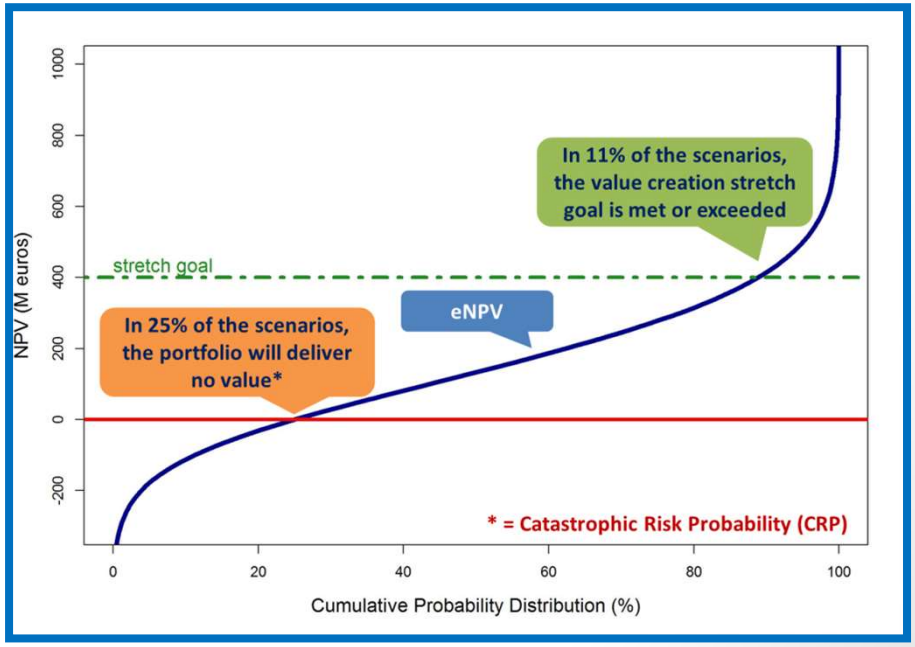
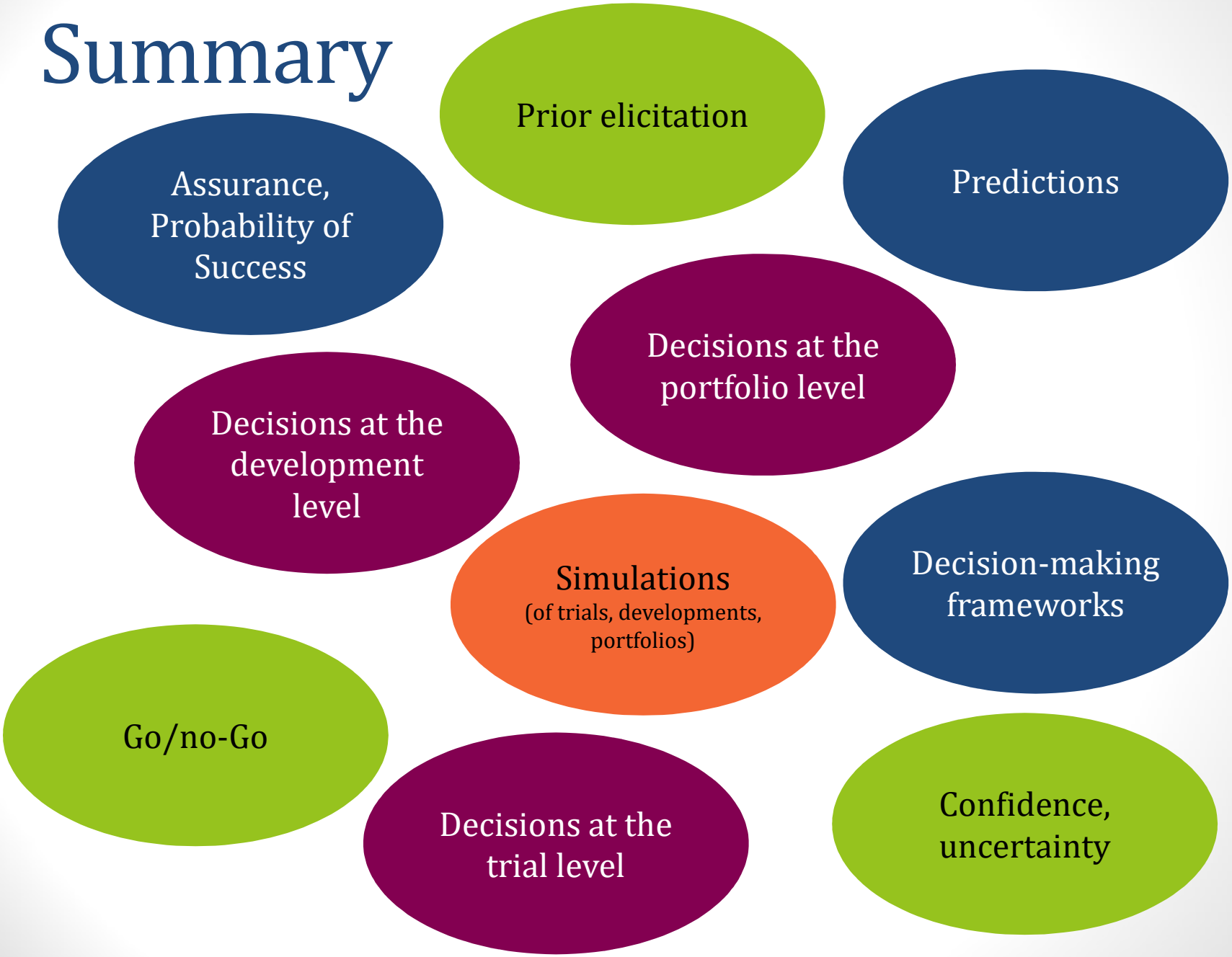
Gaëlle Saint-Hilary

Portfolio financial risk-value profile



Summary


Prior elicitation
Assurance, Probability of Success
Predictions
Decisions at the portfolio level
Decisions at the development level
Simulations
(of trials, developments, portfolios)
Decision-making frameworks
Go/no-Go
Decisions at the trial level
Confidence, uncertainty

Working groups

- **3 working groups** (as of July 2018):
  - Decisions at the **trial level**
  - Decisions at the **development level**
  - Decisions at the **portfolio level**

- **Short-term objective (Q3-4 2018): prepare a survey to collect decision-makers' needs and preferences**

→ **Help from the Stats Leaders to reach our targeted public may be needed!**

- Long-term objectives: literature review, recommendations, develop new methodologies, propose trainings and seminars/webinars (same as for the whole SIG)

1-day EFSPI meeting on decision-making in drug development

- Joint collaboration of our **SIG** and the **EFSPI Scientific Committee (SC)**
- **Organizing Committee**: Emmanuel Quinaux (IDDI, chair, SC), David Wright (AZ, SC), Paul Frewer (AZ, SIG), Guido Thömmes (Grunenthal, SIG), Gaëlle Saint-Hilary (Servier/PoliTo, SIG)
- **When?** Last week of **November** / Beginning of **December**
- **Where?** At **Servier, Suresnes (near Paris)**
- **Who?** Potential speakers include Tony O'Hagan (Sheffield uni.), Paul Frewer (AZ), Nigel Stallard (Warwick uni.), Maria Costa (Novartis), Tom Parke (Berry consultant), Juan Abellan (GSK) + 1 from Health Authorities

Collaboration with the SIG Benefit-Risk

- **Benefit-Risk assessment** is an important aspect of decision-making in drug development
- Activities of our SIGs should not be overlapping

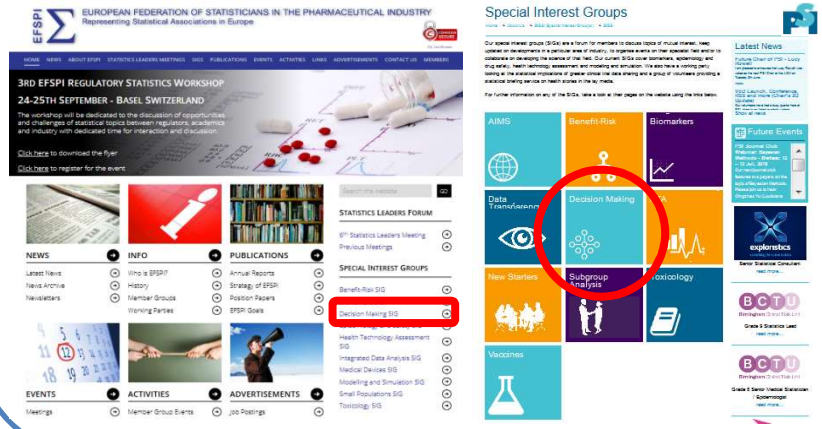
- **Maria Costa** (Novartis), **chair of the SIG Benefit-Risk**, gave a presentation at our SIG meeting on May 3rd 2018
- Post-meeting recommendation: within each working group, each time a method involving both efficacy and safety is identified, **consider a collaboration with the SIG Benefit-Risk**
- Maria Costa will give a presentation at the 1-day EFSPI meeting
- More generally, regular interactions between our SIGs will be planned

Operational aspects

Meetings

- Plenary meetings: one every two months
- Working group meetings: at least once a month

Presentation and contact details on **EFSPI** and **PSI webistes**



Sharepoint provided by Sanofi

PSI would help support activities, promote meetings and webinars, and share other SIG outputs

Conclusion

- Great start!

- **Motivated** and **experienced** team

- Future objectives (2018/2019)
  - Social networking (blog / Twitter / LinkedIn / Facebook…)
  - Webinars
  - Publications?

- Questions? Remarks? Suggestions?