Quantitative Decision-Making in Drug Development

EFSPI Statistical Leaders meeting

July 4th, 2017

Maylis Coste & Sylvain Nicolas

Simple cases, at study level

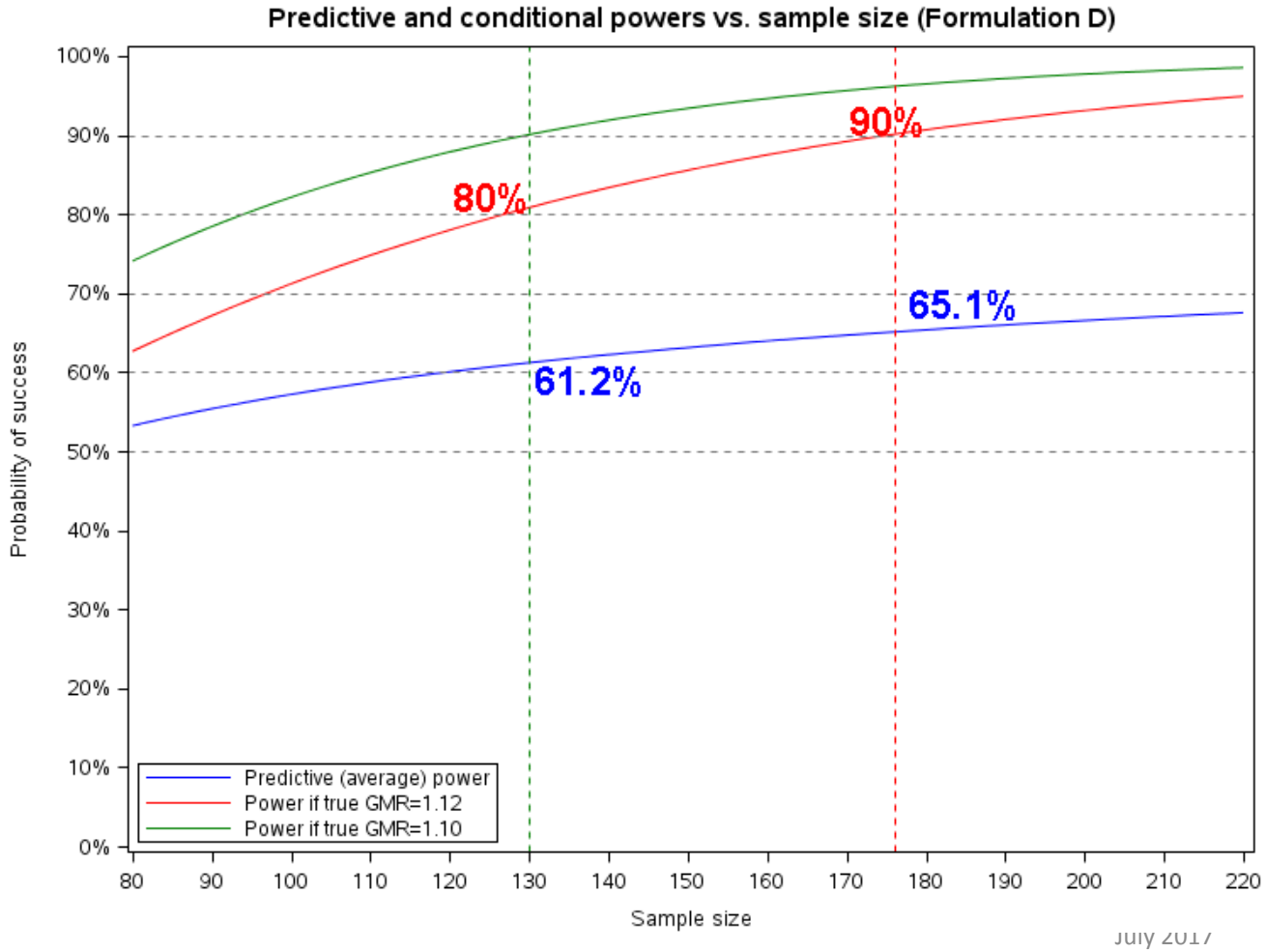
Bayesian PoS for a PK study where variability/uncertainty is high

Assumption :

True ratio assumed to be around 1,12 (with uncertainty as 90%CI= 1,12 [0,93 – 1,35])

SDw assumed around 0,35

Predictive power even lower when using more complex covariance matrices



Objectives

Assess our current practices

Discuss our expectations about the contribution of the statisticians, as well as the Statistical Leaders, into Decision Making

Define how to achieve this together

Decision-making in drug development

At a given **time point**, making an **optimal** choice between **several alternatives** based on the **available information** and **preferences of the decision maker**

Study level
- Choice of the dose
- Population, design (sample size, control arms, duration)
- Stop/continue at interim analyses

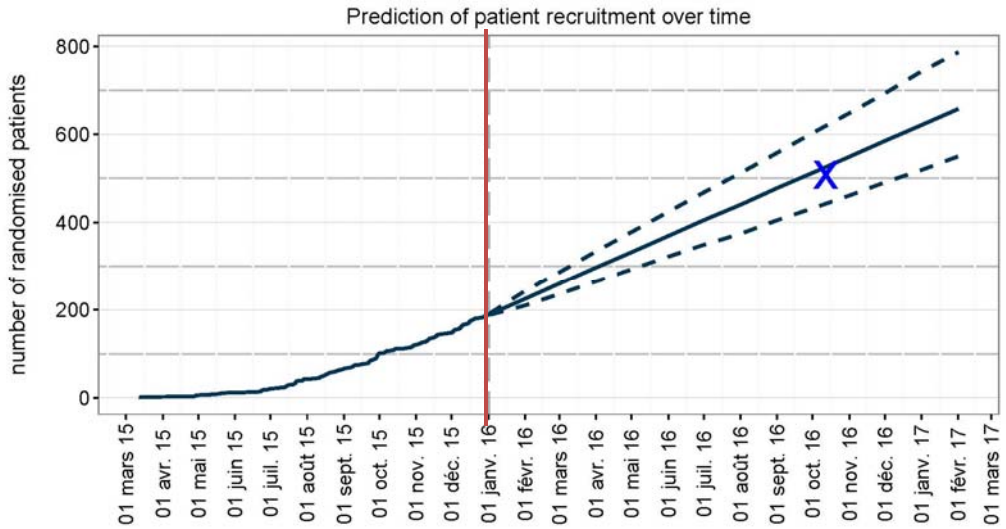
Development level
- Strategy: indication, population, Number of studies, timing of the studies
- Go/No Go at strategic milestones
- Due diligences
- Global project value assessment

Portfolio level
- Go/No Go and selection of the projects
- Resource allocation

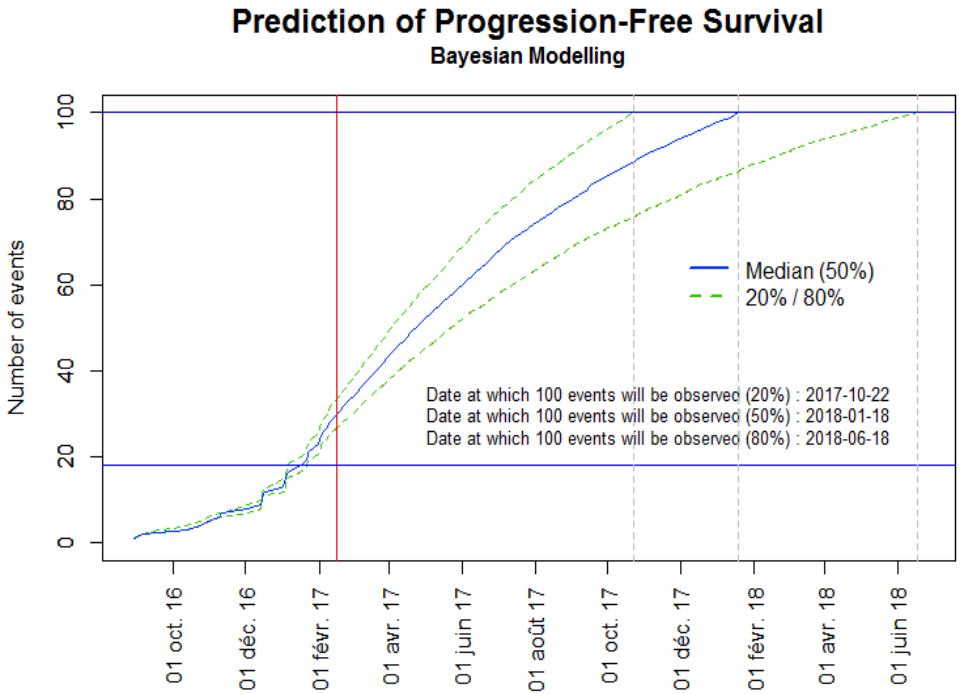
Bayesian modeling for end of study prediction

Recruitment prediction

Date of end of recruitment estimated with a 95%CI



Target nb of events prediction



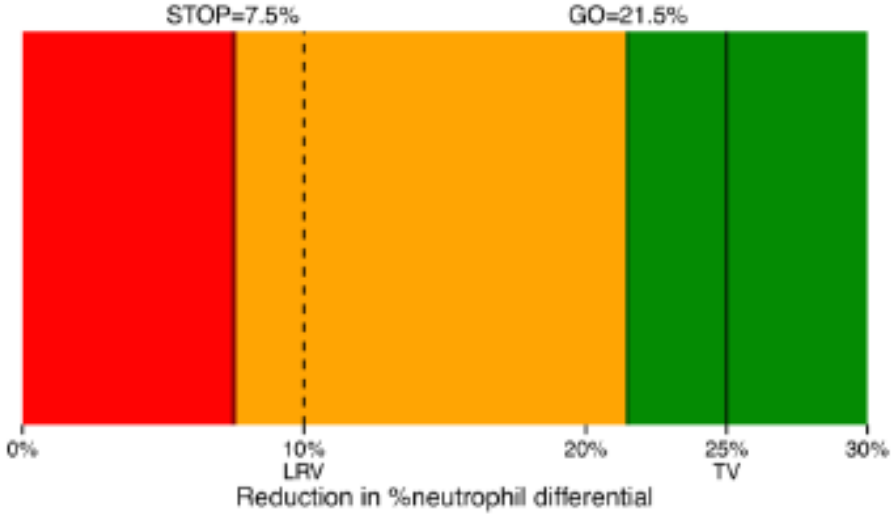
AstraZeneca's decision-making framework

Software developed by Cytel

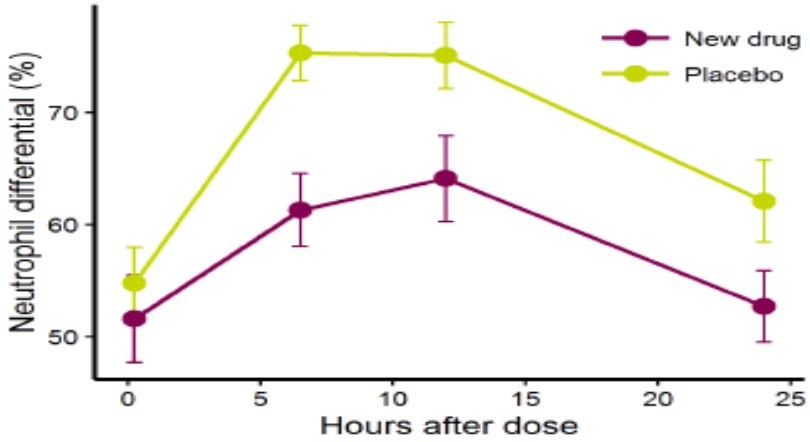
Ex.: Go/No Go criteria for neutrophil differential used as a biomarker for CPOD

1) Decision framework (Go/No Go/Think)

LRV: Lower Reference value – TV: Target value



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



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%

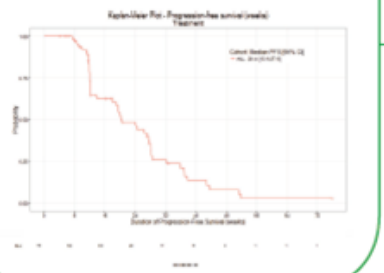
Systematic approach requested by the governance boards in AstraZeneca Early Clinical Development

Source: Taib, Z. and Jauhiainen, A. (2016). *5th Early Phase Adaptive Trials Workshop, Politecnico di Torino, Sep 29 - Oct 1st, 2016*.

Predictive Probability of Success of Phase 3 based on Phase 2 results and historical data (fictive case-study)

Observed results

treatment
Phase II results



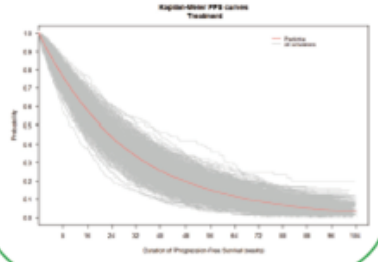
Control
Available Phase II or Phase III results

FDA review		
Study	# events	PFS (weeks)
1	300	16.0
2	100	15.8
3	200	16.3

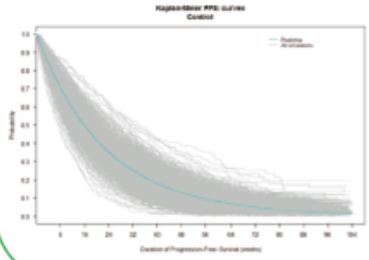
10 000 Clinical Trial Simulations

Predictions

treatment
Predicted Phase III data

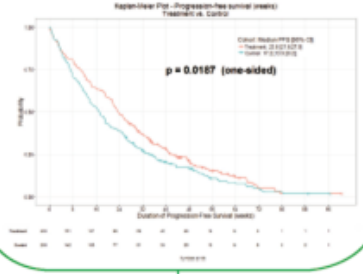


Control
Predicted Phase III data



Comparisons

Comparisons between treatment & Control for each simulated clinical trial



Probability of Success

55%
probability of success*

Go for Phase III

*Proportion of simulated trials with significant p-value

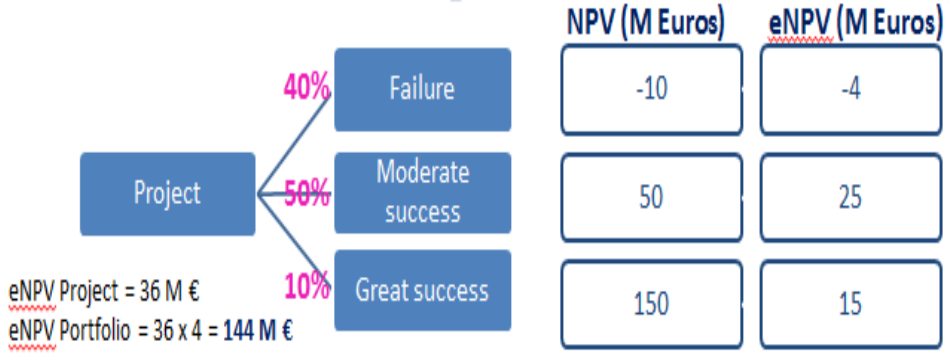
→ **PPoS helps decision-making at strategic milestones**

Comparison of Portfolios

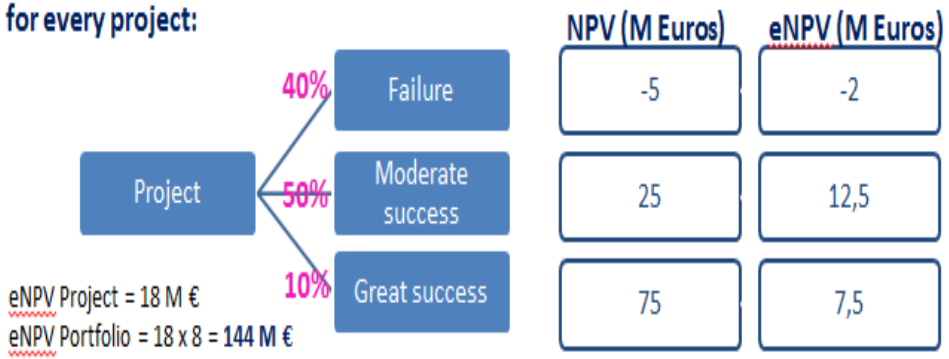
Basic fictive example

Portfolio strategies (with/without partner)

- "Internal portfolio": 4 projects owned internally, with for every project:

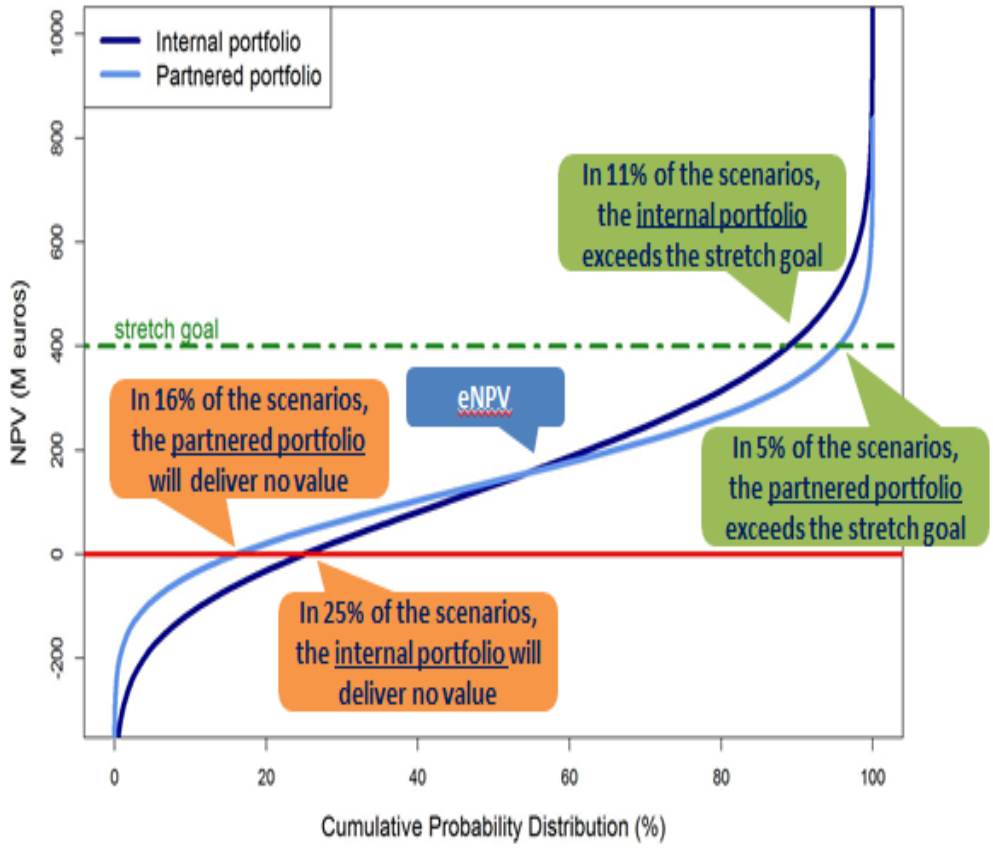


- "Partnered portfolio": 8 projects with 50% of the costs and revenues shared, with for every project:

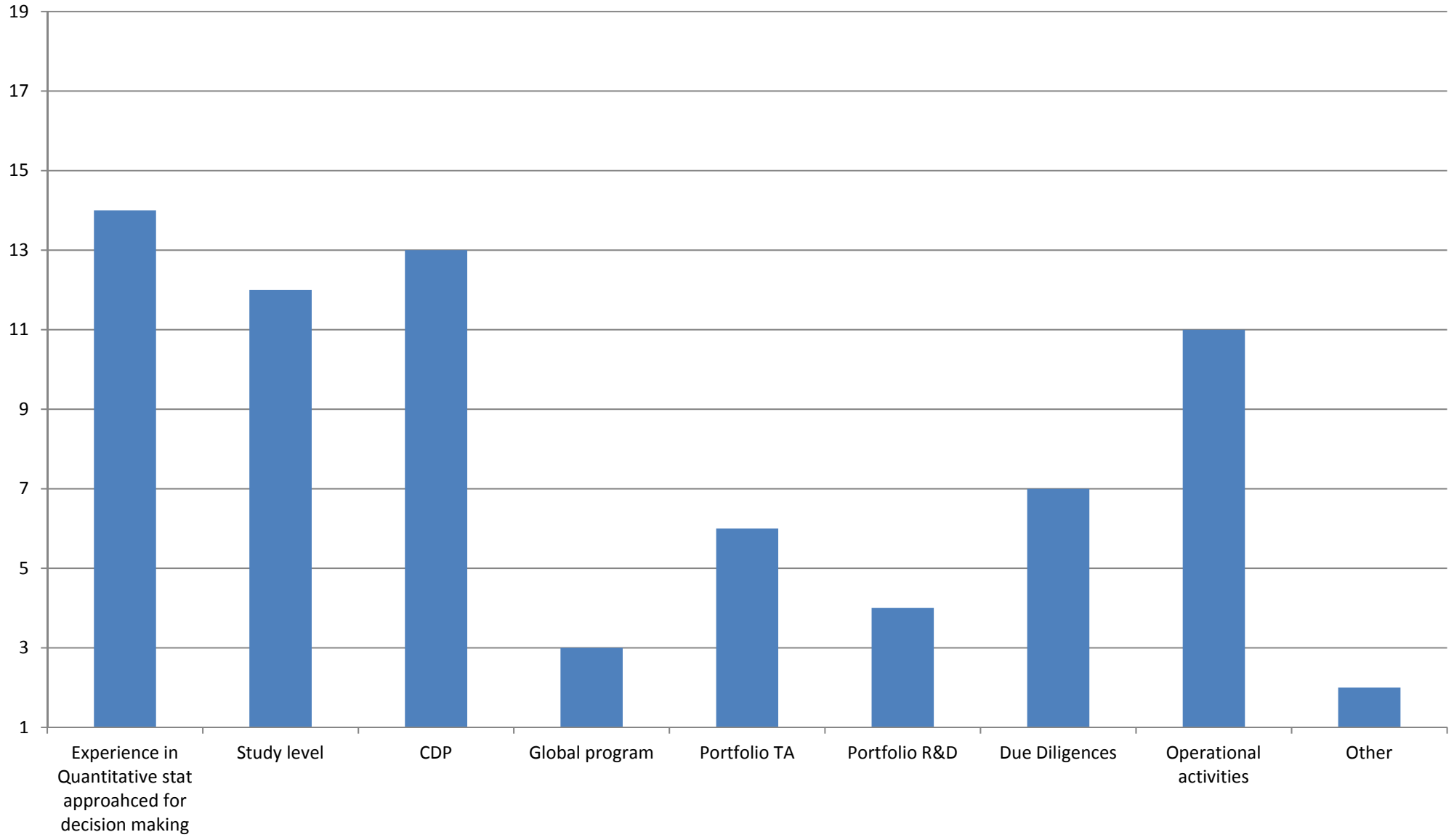


NPV: Net Present Value
eNPV: Expected Net Present Value

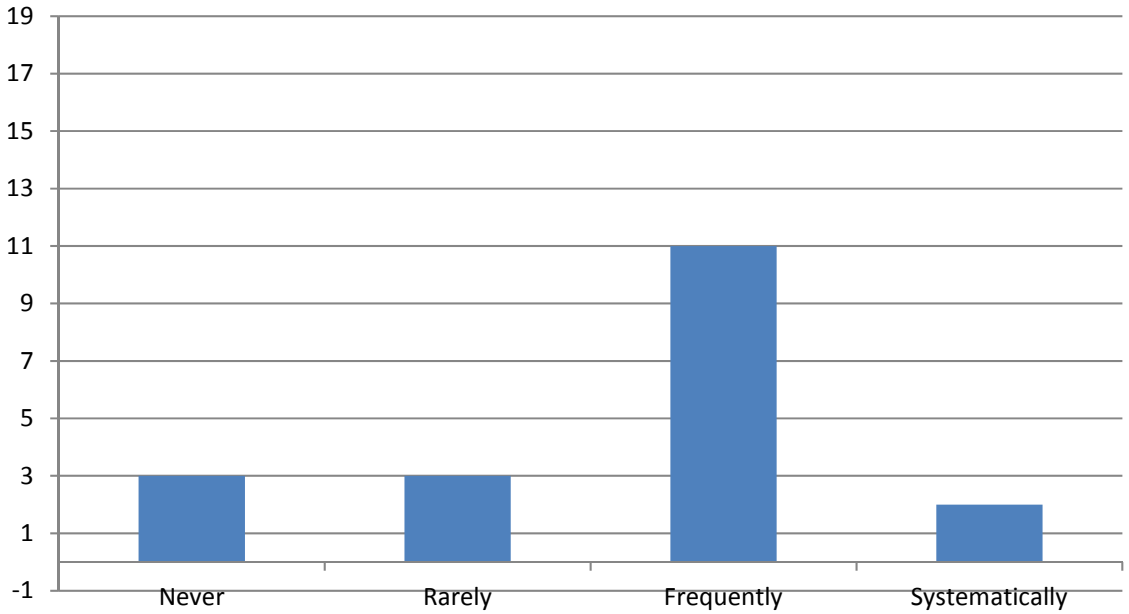
Risk and value profiles



Survey: Use of Quantitative decision making approaches by context

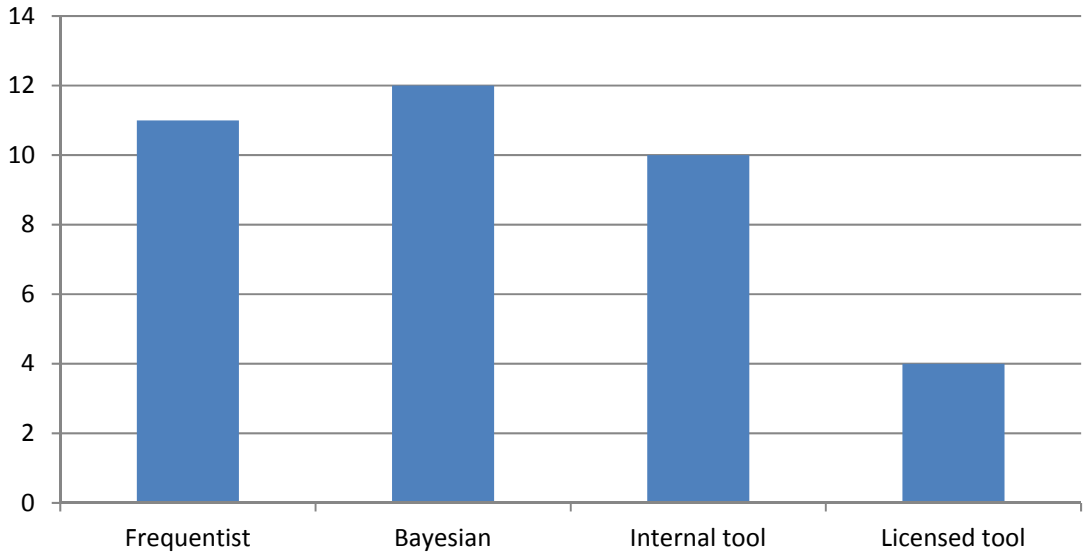


Survey: Frequency, Approaches and Applications



Frequency

Approaches and Applications



Points for discussion

- **Confirm the strategic importance for Statistical teams to develop Quantitative supports for decision making**
- **Promote the position of Statistical teams/leaders to generate Indicators and manage their interpretation and impact**
- **Available for sharing methods and experiences**

- **Support the proposal of an EFSPI SIG to share**
  - Change in mindset/culture and maybe organization
  - Decision criteria
  - Issues, methodologies, statistical methods/tools, interpretation & impacts
  - Examples of applications and stakeholders
  - (Fictive) Case studies and training(s)
  - Leadership : tbd
  - Members: Sanofi, Servier, …….tbd

Bibliography

- **Decision-making framework:**
  - Frewer, P., Mitchell, P., Watkins, C. and Matcham, J. (2016). Decision-making in early clinical drug development. *Pharmaceutical Statistics* 15, 255–263.
  - Lalonde et al. (2007). Model-based Drug Development. *Clinical Pharmacology & Therapeutics* 82: 21—32.
  - A simple way to unify multicriteria decision analysis (MCDA) and stochastic multicriteria acceptability analysis (SMAA) using Dirichlet distribution in benefit-risk assessment, G. Saint-Hilary, S. Cadour, V. Robert, M. Gasparini. *Biometrical Journal* (2017) , 1-12
  - The composite success - Comparing drug development strategies with probabilities of success including benefit-risk assessment to inform decision-making, G. Saint-Hilary, V. Robert, M. Gasparini. *PSI Conf. (2017)*
- **PPoS:**
  - OHagan, A., Stevens, J. W. and Campbell, M. J. (2005). Assurance in clinical trial design. *Pharmaceutical Statistics* 4, 187–201. Gasparini, M., Di Scala, L., Bretz, F. and Racine-Poon, A. (2013). Predictive probability of success in clinical drug development. *Epidemiology Biostatistics and Public Health* 10-1, e8760-1-14.
  - Hong et al. (2012) Predictive power to assist phase3 go/nogo decision based on phase2 data on a different endpoint, *Statistics in Medicine*
  - Saville et al. (2014) The utility of Bayesian predictive probabilities for interim monitoring of clinical trials, *Clinical trials*
  - Ren et al. (2014), Assurance calculations for planning clinical trials with time-to-events outcomes , *Clinical trials*
  - *and Spiegelhalter 1986, Brown 1987, Lecoutre 2001, O'Hagan 2001*
- **Incorporating budget considerations**
  - Antonijevic, Z. (2015). Optimization of Pharmaceutical R&D Programs and Portfolios. Springer International Publishing Switzerland.