EFSPi SIG Quantitative Decision Making

Experience sharing

Gaëlle Saint-Hilary
Co-chair of the SIG
PhD Student, Politecnico Di Torino (Italy) and Institut de Recherches Internationales Servier. (France)

EFSPi Statistics Leaders meeting, 12 July 2018
Outline

- Background, members, objectives
- Examples from the industry: quick overview
- Working groups
- 1-day EFSPSI 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 Quinququis (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

Guido Thömmes

Bayesian decision framework for a PoC trial

- Bayesian approach proposed by Fisch et al (2014)
- The dual criteria will be formulated by means of posterior probabilities
  
  **Significance:** \( \text{Prob}(\text{Effect} > 0 | \text{Data}) > 1 - \alpha \)
  
  **Relevance:** \( \text{Prob}(\text{Effect} > TD | \text{Data}) > 1 - \gamma \).

- The decisions are

<table>
<thead>
<tr>
<th>Relevance</th>
<th>Significance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yes</td>
<td>Go</td>
</tr>
<tr>
<td>No</td>
<td>Go</td>
</tr>
</tbody>
</table>

Guido Thömmes
Examples from 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)
  - $\mu_1 \sim N(0, 0.05^2)$
  - $\mu_2 \sim N(-0.2, 0.05^2)$
  - $\sigma_1^2$ and $\sigma_2^2$ distributions are obtained through the Cochran theorem (inverse-$\chi^2$)

- **Prediction**
  - Test for non-inferiority
  - PoS = 0.91 (Monte Carlo approx.)

---

**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**
  - $P(\Delta \geq 2 | N_1, \pi_1, N_2, \pi_2)$

- **Predictive probability** = 0.356
In 2014, GSK implemented a formal expert elicitation process to translate prior data and expert knowledge into quantitative prior distributions.
Examples from AstraZeneca

Decision-making framework (OKGO)

G. Saint-Hilary

Paul Frewer
Examples from Danone

Decision-making framework at interim analyses

Table 1: Design characteristics simulated on 50,000 trials

<table>
<thead>
<tr>
<th>Sample Size</th>
<th>Step 1</th>
<th>60</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Step 2</td>
<td>130</td>
</tr>
<tr>
<td></td>
<td>Nmax</td>
<td>400</td>
</tr>
<tr>
<td>Interim Analysis Thresholds: CP/p-value (Observed Effect)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>CP for futility</td>
<td>≤5% (2.64)</td>
</tr>
<tr>
<td></td>
<td>Lower CP for SSRE</td>
<td>30% (5.53)</td>
</tr>
<tr>
<td></td>
<td>Upper CP for SSRE</td>
<td>80% (9.04)</td>
</tr>
<tr>
<td></td>
<td>CP for efficacy</td>
<td>99.97% (15.95)</td>
</tr>
<tr>
<td>P-value at final</td>
<td>0.025</td>
<td></td>
</tr>
</tbody>
</table>

Hypothesis:

<table>
<thead>
<tr>
<th>H0</th>
<th>Expected Overall Sample Size E(N)</th>
<th>Pr(Positive trial)</th>
<th>Pr(IncrN)</th>
<th>Pr(Futility)</th>
<th>Pr(No change)</th>
<th>Pr(Eff Stop)</th>
</tr>
</thead>
<tbody>
<tr>
<td>H1</td>
<td>136.1</td>
<td>86.01%</td>
<td>86.29%</td>
<td>23.0%</td>
<td>7.7%</td>
<td>56.9%</td>
</tr>
</tbody>
</table>

*50,000 Trial Simulations with a total planned Sample Size of 136 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

Portfolio financial risk-value profile

Decision-making at the portfolio level
Summary

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

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?