Scientific Advisory Groups (SAG)

Experience and impact of patient involvement

Presented by: Francesco Pignatti
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Training session for patients and consumers involved in EMA activities
25 November 2014
“Our expectations”

Greater involvement of the public, moving away from comitology

Better understanding of regulatory decisions (public explanation of an already made decision)

Participation in decision making by providing different insight (e.g. regulating access via the indication)

‘Permanent’ patient representatives on some EMA committees but not CHMP

Modified from François Houÿez
When to convene a SAG?

- Expected major public health interest where public controversy might be expected (e.g.: first-in-class)
- Substantial disagreement between rapporteurs on clinical aspects
- Controversial issues (e.g., high impact on health care professionals, the public and other stakeholders)
- Complex technical aspects, rare diseases
- Risk minimisation measures affecting the clinical practice
- Design and feasibility of a clinical trial
- Major post-authorisation safety issues

Procedural Advice for CHMP on the need to convene a Scientific Advisory Group (SAG) or *Ad Hoc* Expert Meeting (EMA/CHMP/551508/2010)
Typical Questions for SAG (Oncology)

- Benefit-risk negative or marginally positive
- Clinical meaningfulness of benefits
- Clinical impact of risks
- Need for further studies
- Biologic rationale to support findings
- Guidelines
Company – CHMP – SAG
Communication

SAG

Company presents
(open part of SAG meeting)
Scientific Advisory Groups (EMA/CHMP) vs. Advisory Committees (US FDA)

- Many similarities
  - overall concept, structure, experts
- Key differences

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<thead>
<tr>
<th>FDA: public meetings (recorded, transcript, media)</th>
<th>EMA: not public (but reflected in EPAR)</th>
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<tr>
<td>FDA: generally longer timelines (sponsors’ backgrunder submitted 48 days prior meeting)</td>
<td>EMA: more flexible (min. 2 weeks notice)</td>
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Patient representatives involvement in SAGs

• Statistics for 2013
  – 18/22 (82%) SAG meetings had one or two patient representatives

• Some myths
  – Patients contribution will have little impact
  – Discussion too technical for patients to contribute

➤ 2011 Survey
Are patients able to follow the discussion?

I was able to follow the discussion

Meetings were very informative and interesting

Are patients’ views taken into account?

I feel my comments were taken into account during the discussion

Chairpersons and rapporteurs

The overall impression is that the patient contribution is variable, and can depend on the type of questions addressed during the SAG and on the individual patient who attended;

On the whole, the assessment of contribution ranged from being beneficial (able to obtain patient views with an actual impact on the outcome) to having no actual impact;

In all cases patients were well integrated in the dynamic of the SAGs and the meetings ran smoothly.

Historical perspective on benefit-risk initiatives

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<tbody>
<tr>
<td>PhRMA BRAT</td>
<td>CIRS UMBRA BRAT</td>
<td>CASS/COBRA/SABRE</td>
<td>EMA B-R Methodology Project</td>
<td>FDA Benefit-Risk Framework</td>
<td>WSMI BRAND</td>
<td>IMI Protect WP 5</td>
<td>IMI Advance</td>
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(Modified from M. Ouwens et al., ESFPI/PSI Benefit-Risk Special Interest Group meeting 2013.) Abbreviations: CMR, Centre for Medicines Research International Institute for Regulatory Science; CIRS, Centre for Innovation in Regulatory Science; UMBRA, Unified Methodologies for Benefit-Risk Assessment; EMA, European Medicines Agency; CASS Taskforce of representatives from Health Canada, Australia’s Therapeutic Goods Administration, Swissmedic and the Singapore Health Science Authority; COBRA, Consortium on Benefit-Risk Assessment; PhRMA BRAT: Pharmaceutical Research and Manufacturers of America Benefit-Risk Action Team; BRAND, Benefit-Risk Assessment for Nonprescription Drugs; IMI PROTECT, Innovative Medicine Initiative "Pharmacoepidemiological Research on Outcomes of Therapeutics by a European ConsorTium"; Advance, "Accelerated development of vaccine benefit-risk collaboration in Europe".)
Benefit-risk assessment toolkit

All B-R assessment approaches

Approaches excluded and not appraised

Benefit-risk assessment framework

Metric indices for B-R assessment

Estimation techniques

Utility survey techniques

Descriptive framework

Quantitative framework

Threshold indices

Health indices

Trade-off indices

Legend:

Main categories

Sub-categories

ProACT-URL
ASF
BRAT
FDA BRF
CMR-CASS
COBRA
SABRE
UMBRA

BLRA
NCB
Decision tree
MDP
MCDA
SMAA
SBRAM
CUI
DI

NNT
NNH
AE-NNT
RV-NNH
Impact numbers
MCE
RV-MCE
MAR
NEAR

QALY
DAILY
HALE
Q-TWIST

UT-NNT
INHB
BRR
GBR
Principle of 3
TURBO
Beckmann

DAGs
PSM
CPM
ITC
MTC
CDS

SPM
CV
CA
DICE

IMI PROTECT Work Package 5
Different views about quantitative methods

<table>
<thead>
<tr>
<th>Against</th>
<th>In favour</th>
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<tr>
<td>Require more effort</td>
<td>Easy to update</td>
</tr>
<tr>
<td>Does not reflect mental process</td>
<td>Intuition can lead to error and bias</td>
</tr>
<tr>
<td>Highly subjective</td>
<td>No more subjective than any other decision-making strategy</td>
</tr>
<tr>
<td>“Black box”</td>
<td>Subjectivity is handled explicitly</td>
</tr>
<tr>
<td>High precision is unattainable</td>
<td>Easily understood, transparent</td>
</tr>
<tr>
<td>Oversimplification (“single number”)</td>
<td>Uncertainty can be managed explicitly</td>
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<tr>
<td>Whose values? The authority of the decision-makers will be questioned</td>
<td>Impact of different inputs (e.g., from patients) can be explored. Regulator’s decisions can be scrutinised.</td>
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MCDA to elicit stakeholder’s preferences based on regulators’ assessment

EMA workshop with PCWP and HCPWP (26 February 2014)

Separate, parallel exercise with patient jury and healthcare professionals jury

Two hours to build 2 models using MCDA (MACBETH - Measuring Attractiveness by a Categorical Based Evaluation Technique)

Hypothetical example:

- Vandetanib in medullary thyroid cancer

### Vandetanib in MTC: Efficacy

**Note:** Hypothetical example modified from Vandetanib EPAR; presented data are not necessarily accurate or complete.

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<tr>
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<th>Placebo</th>
<th>Vandetanib</th>
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<tr>
<td>Progression-free survival (median months)</td>
<td>19.3</td>
<td>30.5</td>
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<tr>
<td>Objective Response Rate</td>
<td>13%</td>
<td>45%</td>
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![Graph showing progression-free survival](image)
Patient Jury Results: Vandetanib

CHMP: improvement in PFS, ORR ... are of importance ... The management of the risk of QT prolongation ... are particularly important. Benefits outweigh the important risks outlined.
Decision Analysis Modelling (MCDA)

Hypothetical example

5. Sensitivity Analysis
6. Scenario Analysis...
(explore various scores/weights)

![Graph showing an example of sensitivity analysis](image)
Conclusions

• SAGs: important tool for bringing patients’ values and preferences into the system
  – Overall interactions with patients groups have proved useful;
  – They bring a crucial patient perspective to the discussions on medicinal products
  – Can help to provide valuable insights such as acceptable levels of associated risks

• Methods to elicit patient preferences are being piloted