Benefit/risk – patient/engagement

Anne Lee, Chief Pharmaceutical Adviser, Scottish Medicines Consortium
Richard Huckle, Senior Consultant, Pope Woodhead
When, why, what…. Benefit–risk?

• It’s not new?
  • Benefit–risk (or risk-benefit as it was then) evaluations of drugs have been conducted since the introduction of modern regulatory systems in the 1960s

• Past decade or so
  • Both industry and regulators have started to focus on the actual methodology for conducting such BR evaluations

• So what?
  • Regulators take decisions on behalf of patients and prescribers

• Decision-making
  • Subjective process - influenced by many factors

• Challenges
  • Regulators challenged by patients, patient organisations, health care professional and industry…. also media and politics

To meet challenges decisions made need to be consistent, transparent, and objective
**Is benefit-risk the convergence point for patient-focused drug development?**

**Benefit-risk assessment** - The comparative evaluation or weighing of benefits (positive effects) and risks (potential harm) of various medical options for treatment, prophylaxis, prevention or diagnosis.

All stakeholders - importance of the patient’s point of view fully acknowledged. 

- **Patients / Carers**
  - Make decisions for themselves / patients

- **Healthcare providers**
  - Make decisions based on prescribing lists

- **Health Technology Assessors / Payers**
  - Make decisions on cost-effectiveness etc

- **Regulators**
  - Make decisions on quality, safety, efficacy and benefit-risk balance to individuals and public health

- **Pharmaceutical companies**
  - Make decisions on what to develop for which licenses to apply

Individuals may perceive or weigh benefits and/or risks differently depending on their personal preference, progression or regression of disease, social standing, value etc etc ......

Adapted from http://www.protectbenefitrisk.eu
Is benefit-risk the convergence point for shared decision-making?

• **Models for regulator and payer collaboration**: discussions held in several fora to promote various forms of collaboration including parallel advice during development, with the underpinning desires to:
  
  • a) coordinate and/or streamline systems and processes to speed up decisions and patient access and if possible reduce the burden for industry
  
  • b) define the roles of the different bodies in assessing comparative effectiveness

• **Patient engagement**: Value of individual expert patients versus virtual patient communities – potential to democratise drug development? Role for ‘disruptive technologies’?

• **Organisational change**: Is BR a model for industry, regulators and payers to align with the aim of benefiting patients and still achieve compliance? Or should BR be put at the side as just another regulatory hurdle? Does your organisation/way of thinking need to change to reflect this?
The approval/access landscape has shifted, requiring an integrated approach to address multiple stakeholder needs.

**Traditional**
- Regulators making access decisions
- Regulator decisions based on safety, quality and efficacy
- Conditional MA
- Risk Management Plan
- Scientific Advice
- CRF/patient diary
- BR assessment (IB + clinical protocol)

**Evolving**
- Regulators and HTA bodies making access decisions
- Benefit-risk balance: the cornerstone of the regulatory approval process
- Early access/adaptive pathways/PRIME/BTD
- BR management plan
- Parallel advice
- PRO/ePRO
- CTD Clinical Overview ICH M4E(R2)
Changing interface between different decision maker requires an evolving development strategy

### Traditional

**MA**
- Regulators
  - Quality, efficacy, safety
  - BR profile
- HTA/payers
  - Relative efficacy / effectiveness
  - Cost versus health benefit
  - Budget impact
- RCT – placebo (most often)

### Evolving

**MA**
- Regulators
  - Quality, efficacy, safety
  - BR profile
- HTA/payers
  - Relative efficacy / effectiveness
  - Cost versus health benefit
  - Budget impact
  - Dedicated relative efficacy / effectiveness assessment
- RCT – placebo and comparator
  - Cost effectiveness / utility analysis
  - Budget impact analysis
- RCT – adaptive III/IV
  - Observational studies
  - Meta analysis

But will BR help HTABs and regulators agree? – Optimise patients access to medicines

How aligned are the perspectives of EU regulators and HTA bodies? A comparative analysis of regulatory-HTA parallel scientific advice (based on 31 procedures). n represents the total number of HTABs expressing an opinion for each domain.

![Bar chart showing percentage of full agreement, partial agreement, and disagreement across different domains such as population, comparator, endpoints, study design characteristics, and overall efficacy and safety data package.]

History suggests they won’t! Will PSA help them to agree or compromise?

Benefit-risk discussions with relevant decision makers for the specific issues along a product lifecycle

**Aim**

- Generate data that meets needs of all stakeholders as efficiently as possible – preferably in one trial design/one development plan
- Avoiding excess burden on patients
- Prevent avoidable/methodological reasons for failure later
- Without additional requirements
- Understand views/needs of each others and the divergences
- To find the solutions/third way
- Not forcing agreement and adhere to remits
Another reason why BR has come to the fore - it has become a CTD requirement

- The Common Technical Document (CTD) is the point of reference for regulatory decisions during a Marketing Authorisation Application review
- Global approach for presenting product BR information in filing for approval
- M4E(R2) revised guideline adopted by ICH in June 2016

Section 2.5.6 Benefits and Risks Conclusions

2.5.6.1 Therapeutic Context
   2.5.6.1.1 Disease or Condition
   2.5.6.1.2 Current Therapies

2.5.6.2 Benefits
   Describe key benefits (major efficacy endpoints; may also include combination endpoints, important characteristics)

2.5.6.3 Risks
   Describe key risks (subset of ‘important risks’) and how they will be managed

2.5.6.4 Benefit-Risk Assessment
   Summary and explanation of B-R conclusions, interpreting data from the previous subsections. May include tables and graphical displays

2.5.6.5 Appendix
   Presentation of more detailed B-R methodology

No prescribed approach for the assessment
Each benefit-risk assessment impacts a variety of downstream deliverables for multiple stakeholders

**Industry**
- Agree B-R ownership
- Produce TPP
- Refine and test TPP
- Develop and update DRMP
- Prepare MAA, CTD B-R section 2.5.6
- Implement Registry, studies
- Agree & develop Risk Minimization Strategy & Measures (RMMs)
- Add’l evidence gen. strategy (PV plan)
- EU-RMP & RMM updates
- RMM effectiveness eval.
- Prepare DSUR
- Update DSUR
- Update DSUR
- Produce/update PBRER
- Implement Registries, studies
- RWE for regulators/payers
- Clinical study approvals

**Regulators**
- Qual pricing research
- Early value proposition
- Early economic model
- Develop scientific communication plan
- MEA (finance/outcome-based) strategy
- Develop & update Investigator’s Brochure
- User test RMMs
- Implement HCP RMMs
- Quant pricing research
- GVD; BI/CE models
- Payer education/engagement tools
- Impact and refinement - TPP
- Implement Registry, studies

**Payers**
- Prepare drug label
- Prepare MAA, CTD B-R section 2.5.6
- Develop EU-RMP, REMS, etc.
- Agree & develop Risk Minimization Strategy & Measures (RMMs)
- Add’l evidence gen. strategy (PV plan)
- EU-RMP & RMM updates
- RMM effectiveness eval.
- Prepare DSUR
- Update DSUR
- Update DSUR
- Produce/update PBRER
- Implement Registries, studies
- RWE for regulators/payers
- Clinical study approvals

**HCPs / Investigators**
- Develop & update Investigator’s Brochure
- User test RMMs
- Implement HCP RMMs
- KOL engagement plan

**Deliverable finalization**
The patients voice can now be heard during regulatory decision-making processes

Any organisation representing EU patients or consumers can express interest to work with EMA

Three categories of patient participation:
1. Member, alternate or observer
2. Individual patient expert
3. Representative of an organisation
The era of patient-centricity
- Patient involvement in the clinical trials continuum extends beyond advisory committees

Clinical study set-up
- Eligibility criteria (study protocol)
- Assist with:
  - informed consent
  - Study recruitment
  - Study steering committee

Programme level
- Data Safety Monitoring Board
- Report study experience

Regulatory advice
- Serve on advisory committees (e.g. CAT, CHMP, PDCO, PRAC, COMP – SAG)

Pre-study
- Development plan/TPP
- Study start-up
- Study conduct
- Analysis and dissemination
- Regulatory review and approval
- Post-approval

During regulatory assessment
- Provide feedback:
  - Public Summaries of Opinion
  - Package Leaflets (PLs) and EPAR summaries
  - User testing RMMs

• PAS design (expectations of patient community)
• Serve on post-market surveillance initiatives
• Share product information with patient community
• Feedback on renewals and variations

Potential risk of being perceived as engagement with promotional intent?

Adapted from Parkinson’s Disease Foundation materials, developed by the Clinical Trials Transformation Initiative and Reflection Paper on the use of patient reported outcome (PRO) measures in oncology studies - Pignatti, et al. Mol Oncol. doi: 10.1016/j.molonc.2014.10.003
## EMA activities involving patients and consumers as individual experts

<table>
<thead>
<tr>
<th>Activities involving individual experts</th>
<th>Number of Experts</th>
<th>Activities involving individual experts</th>
<th>Number of Experts</th>
</tr>
</thead>
<tbody>
<tr>
<td>Review of documents</td>
<td></td>
<td>Focus group with Myeloma patients</td>
<td>10</td>
</tr>
<tr>
<td>Herbal summaries</td>
<td>29</td>
<td>Myeloma UK focus group</td>
<td>11</td>
</tr>
<tr>
<td>EPAR summaries</td>
<td>36</td>
<td>First conference call with Myeloma UK</td>
<td>1</td>
</tr>
<tr>
<td>Package Leaflets</td>
<td>60</td>
<td>Second conference call with Myeloma UK</td>
<td>1</td>
</tr>
<tr>
<td>Safety communications</td>
<td>26</td>
<td>Clinical data publication</td>
<td></td>
</tr>
<tr>
<td>Involvement in medicines evaluation / committee consultations</td>
<td></td>
<td>User testing of clinical data publication website prototype - 7 July</td>
<td>4</td>
</tr>
<tr>
<td>PRAC product-related consultation</td>
<td>5</td>
<td>User testing of clinical data publication website prototype</td>
<td>4</td>
</tr>
<tr>
<td>CHMP product-related consultation</td>
<td>13</td>
<td>Meetings with patients</td>
<td></td>
</tr>
<tr>
<td>CHMP consultation on labelling and package leaflet of emergency contraceptives</td>
<td>13</td>
<td>Meeting with patients on rheumatoid arthritis</td>
<td>3</td>
</tr>
<tr>
<td>EMA/PRAC consultation on product (brochure for individuals/reminder card)</td>
<td>2</td>
<td>EMA meeting with erythropoietic protoporphyrha</td>
<td>18</td>
</tr>
<tr>
<td>PRAC consultation on product related educational material</td>
<td>5</td>
<td>Meeting on shortages - myeloma products</td>
<td>2</td>
</tr>
<tr>
<td>QRD/PRAC written consultation on risk minimisation of medication errors</td>
<td>3</td>
<td>CHMP oral explanation (pilot project)</td>
<td></td>
</tr>
<tr>
<td>Scientific advice/protocol assistance/scientific advice with HTA:</td>
<td>82</td>
<td>CHMP Oral Explanation on Kyndrira (dissapersen)</td>
<td>3</td>
</tr>
<tr>
<td>Patients attending committees’ meetings as experts</td>
<td>8</td>
<td>CHMP Oral Explanation on Ataluren</td>
<td>3</td>
</tr>
<tr>
<td>Participation in SAGs/Ad hoc expert group meetings</td>
<td>28</td>
<td>CHMP Oral Explanation on Ataluren</td>
<td>4</td>
</tr>
<tr>
<td>Review of package leaflet wording (class labelling revision HIV medicines)</td>
<td>3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Review of urea cycle disorders medicine supply issues (Art. 31 referral)</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>TOTAL</strong></td>
<td><strong>433</strong></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### Training

- Patient training day: 43
- Webinar on review of herbal summaries: 5
- Training modules from the EudraVigilance training curriculum (ADR e-learning): 6
- Benefit-risk methodology project: | 1

---

**Patient and Consumer involvement in EMA activities (2009-2016)**

![Bar chart showing involvement in EMA activities over time](chart.png)
Developments in technology have resulted in the creation of new tools with potential to add significantly to the BR assessment over an entire lifecycle.

**Determine B/R**
- Quantitative signal detection
- Patient preference studies

**Support patients & prescribers**
- Educate & share
  - Company-sponsored
  - Websites, blogs etc
- Improve patient experience
  - Awareness & reminder apps
  - Manage treatment
  - Biometric apps
- Improve prescriber experience
  - Opinion networks
  - Diagnostic tools and apps
- Measure change & behaviour
  - Wearable & sensors
  - Technology-enabled Analytics

**Regulatory compliance**
- Justified, validated and evaluated
- CE marked?

Potential risk of being perceived as engagement with promotional intent?

https://doi.org/10.1371/journal.pmed.1001953
http://journals.plos.org/plosmedicine/article?id=10.1371/journal.pmed.1001953
Should BR be the convergence point? - How is BR viewed in your organisation?
Patients no longer guinea–pigs in drug development?

Integrated approaches aligning HTA/payer and regulatory requirements - optimising patient access

A collaborative approach will continue to advance the science