EFSPI Benefit-Risk SIG Blueprint and update

-Current status

-Next steps

Ian Hirsch

On behalf of the EFSPI/PSI BR SIG

EFSPI Statistical Leaders Meeting

18th June 2013

EFSPI Benefit-Risk SIG

Reminder-Main aims of the SIG

The main aims of the Benefit-Risk Special Interest Group are split into 5 key areas

1. To understand how best to **apply Benefit-Risk Methodologies** across the Pharmaceutical Industry including processes for implementation, issues that arise and recommendations

2. To **share examples** of how Benefit-Risk has been used within pharmaceutical companies, any best practices arising from them and how they can best be used from an industry perspective across all phases of development and post licensing. Examples include portfolio decision making and key regulatory documents such as Development/Periodic Safety Update Reports

3. To discuss and **make recommendations** on key methodological issues for example utility functions and weighting approaches

4. To **share external information** including new developments around Benefit-Risk including those in the literature and outputs from Benefit-Risk initiatives and to produce guidance on how best they can be used within the EFSPI arena

5. *Outputs from the first 4 areas will then be used to **inform, educate and pass on learning** for those within EFSPI and its affiliations of what information is available, proposed best practices, implementation guidelines/processes together with information on different methodologies via various forums such as an EFSPI Benefit-Risk website/WIKI and supporting specific Benefit-Risk meetings.*

EFSPI Benefit-Risk SIG
Reminder-Vision

Within 2-3 years EFSPI members will have access to material to increase their capability within the area of structured Benefit-Risk by sharing the most up to date B-R information based on outputs from the SIG

EFSPI Benefit-Risk SIG
Membership and thanks

Ian Hirsch (AstraZeneca-chair of SIG)
Susan Shepherd (Amgen)
Martin Gebel (Bayer)
Rebecca Sudlow and George Quartey (Roche and George link to epidemiology/safety SIG & QSPI)
Guenter Heimann and Ekkehard Glimm (Novartis)
Maylis Coste and Veronique Robert (IRIServier)
Dan Evans (Pfizer)
Yunxia Lu (Karolinska Institutet)
Alan Phillips (Icon)
Alberto Garcia-Hernandez (Astellas)
Alexander Schacht (Eli Lilly)
Mario Ouwens (Abbott)
Shahrul Mt-Isa (Imperial College)
Del Jones (GSK)

In addition Andrew Thomson from the MHRA is not officially a member but attends the SIG meetings.

EFSPI Benefit-Risk SIG

Aims for today

EFSPI Statistical Leaders input/advice

- Blueprint
- Draft findings from outputs
- Next steps
- Request to EFSPI Stats Leaders

EFSPI Benefit-Risk SIG

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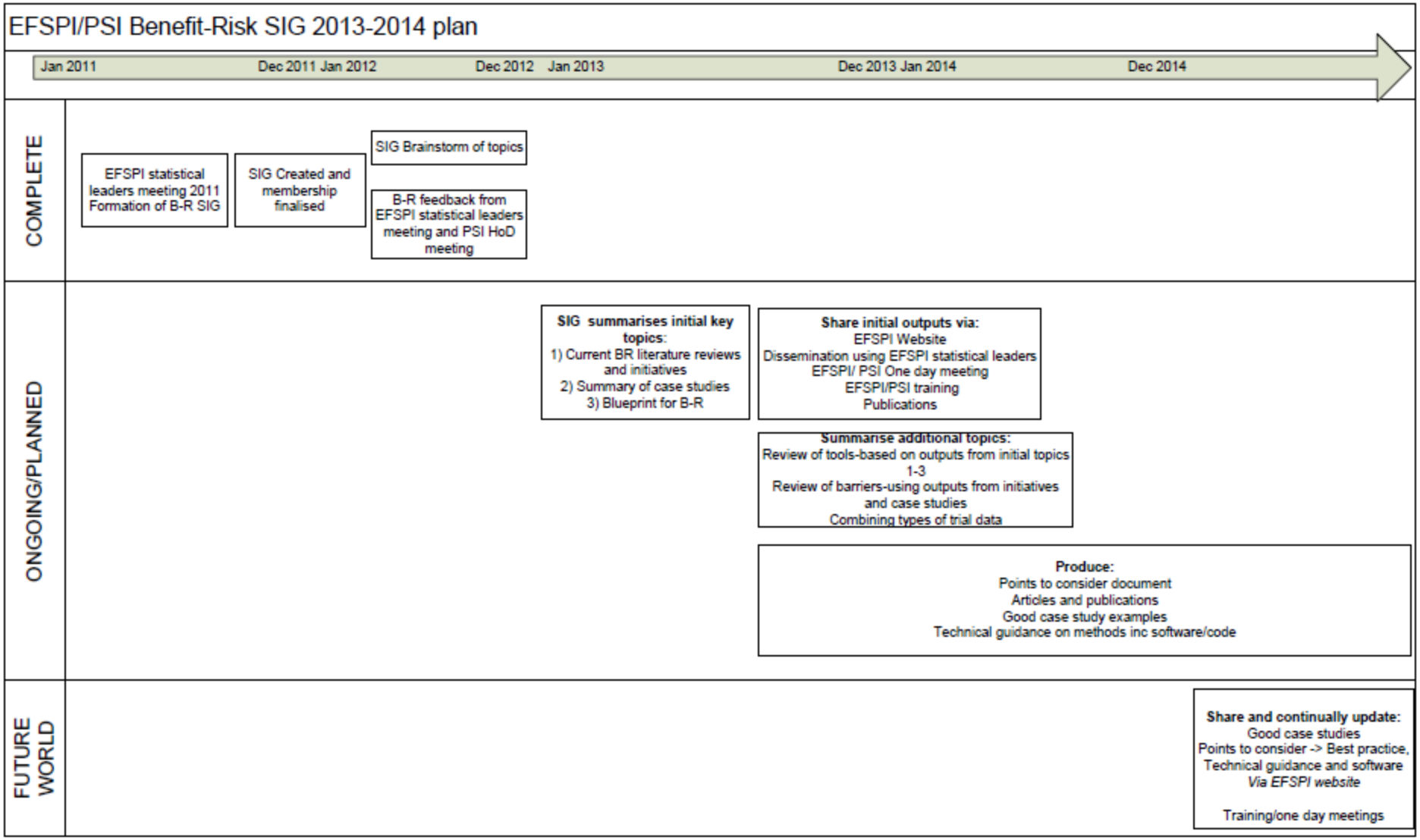
EFSPI Benefit-Risk SIG
Blueprint-Timings



EFSPI Benefit-Risk SIG
Blueprint-Scope

- In Scope
  - Structured benefit risk assessments in order to **aid transparency** of assessments
    - Pre-planned, systematic and includes comparisons with key competitors
  - Points to consider on carrying these out based on **experiences**
    - Including standard terminology and needs to be evolving
    - Cyclic nature and aims to start at least at phase 2
  - Summary and how to carry out **different methodologies**
    - Both qualitative and quantitative
  - Sharing of **case study** examples
  - **Stakeholders** to include regulatory and payer
  - Points to consider based on **lessons learnt** and on **where statisticians can input** into these assessments
  - Helping to describe resource estimates including efficiencies with other internal processes
    - Such as how risk management plans are developed pooled analyses plans for registration, meta analyses/modelling of internal and external data for decision making
  - **Barriers** that might be encountered

EFSPI Benefit-Risk SIG
Blueprint-Out of Scope

- Out of scope
  - **Company strategy** such as whether to use quantitative or qualitative methods
  - **Guidance** as it is too early in implementation

EFSPI Benefit-Risk SIG
Outputs

1. Evolving **points to consider** based on experiences and lessons learnt
   - Needs to be continuously updated with experiences
   - Needs to include standard terminology for SIG
   - Learnings from different implementation approaches with pros and cons
     - Using pilots
   - To include examples of where statisticians can input into and lead B-R assessments
     - Such as meta analyses of internal/external data, facilitating choice of benefit/risks to use, incorporating different methodologies (including utilities and weighting)
   - Could include suggestions from a regulatory perspective

2. A set of example **case studies**

3. Links to **key publications/reviews and initiatives** and outputs from the literature

EFSPI Benefit-Risk SIG

Outputs

4. **Publications-** for example
   - Based on conducting interviews of experiences across companies including what has worked well, learnings and difficulties (as done for BRAT framework)
   - Based on our outputs
     - Case studies
     - Literature summary/initiatives

5. **Technical and methodological guidance** inc software/code
   - can be a link to external work

EFSPI Benefit-Risk SIG
Communication strategy

A general communication strategy is useful both for delivery of outputs now but more importantly how we keep communication going in the future with positive examples.

- Initial strategy to include
  - Training course
    - to incorporate why we should carry out structured BR, the theoretical aspects and lots of examples
  - Different publications based on our outputs
  - Articles in newsletters, society magazines
  - Putting on sessions at conferences and one day meetings
  - Working through EFSPI statistical leaders

- The EFSPI website will be used as a home for both SIG information sharing but also to share more broadly

EFSPI Benefit-Risk SIG

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Benefit-Risk Special Interest Group

What we have done…

Group 1 and 2: Literature reviews on different methods and summaries of initiatives

Mario, Martin, Shahrul, Alexander, Véronique and Maylis

Group 3: Collect good case studies to share from either companies and initiatives

Alberto, Susan, Rebecca, George

Group 4: Working on a blueprint of the how statisticians can play a leading role in Benefit-Risk and a strategy for sharing the first 3 groups outputs

Ian, Andrew, Guenter, Alan and Del

Current outputs available on EFSPI/PSI website

Benefit-Risk Special Interest Group

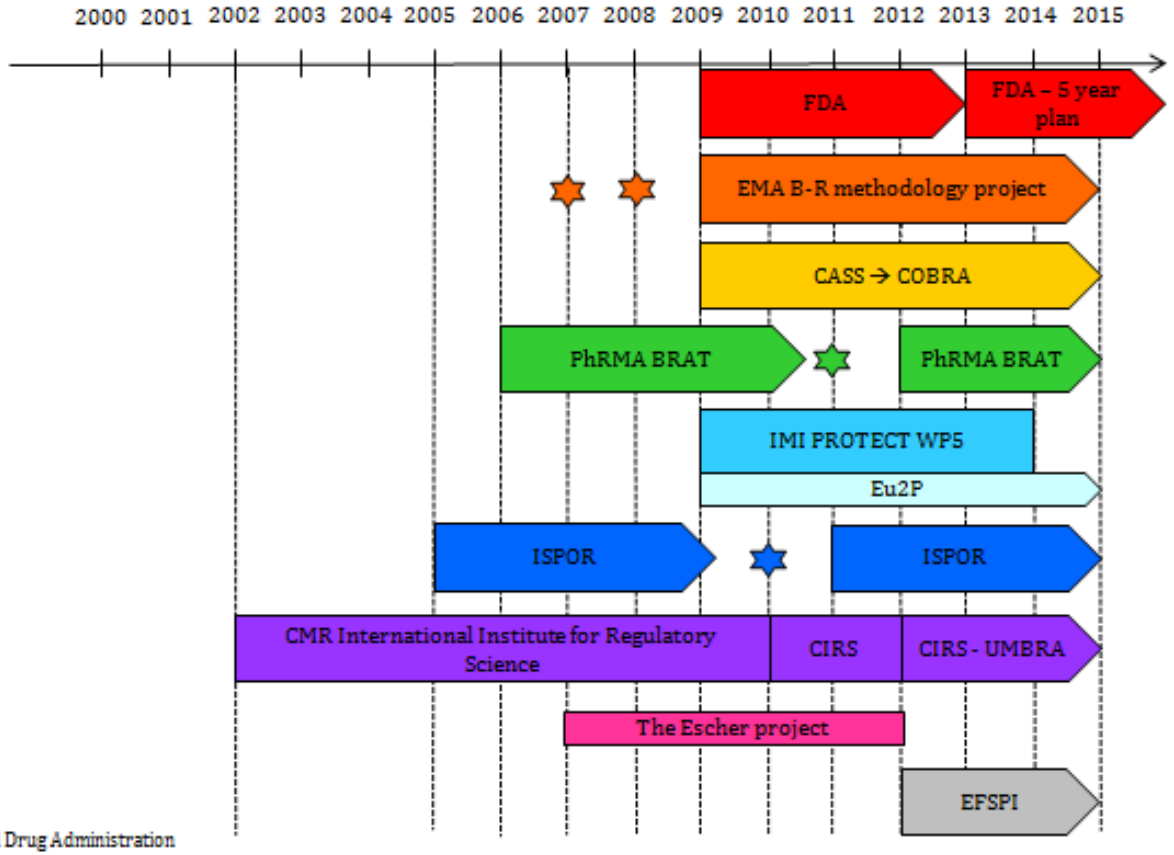
Highlights

Group 1 and 2 : Literature reviews on different methods and summaries of initiatives

- Summary and timings of different initiatives and conclusions
- Review of key literature (40 reviews found) and findings
- Key literature summarised
- Given overlap of reviews and initiatives a single output is being produced

- *QSPI B-R workgroup recently set up*

Overview of the initiatives since 2000



- *FDA*: Federal Drug Administration
- *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
- *IMI PROTECT*: Innovative Medicine Initiative Pharmacoepidemiological Research on Outcomes of Therapeutics by a European ConsorTium
- *Eu2P*: European programme in Pharmacovigilance and Pharmacoepidemiology
- *ISPOR*: International Society for Pharmacoeconomics and Outcomes Research
- *CMR*: Centre Medical Research
- *CIRS*: Centre for Innovation in Regulatory Science
- *UMBRA*: Unified Methodologies for Benefit-Risk Assessment
- *EFSPI*: European Federation of Statisticians in the Pharmaceutical Industry

Summary of initiatives-findings

- There is a consensus about the **qualitative framework**: it is needed to permit a structured benefit-risk assessment and plays a fundamental role in assisting and improving decision making.

- Several **quantitative methods** with different purposes (estimation techniques, metric, utility techniques) were reviewed. Among them, MCDA, NNT & NNH, INHB, probabilistic simulation, Bayesian approach are the most common.

- Communication using graphical tools is an important part of benefit-risk assessment.

- The different working groups also work on the integration of patients' preferences in benefit-risk assessment

Key publications

Nice point of starting to read about benefit/risk assessment:

- EMA
  - Benefit-risk methodology project: Work package 2 report: Applicability of current tools and processes for regulatory benefit-risk assessment
- BMC
  - A framework for organizing and selecting quantitative approaches for benefit-harm assessment

Very important for statisticians

- ISPOR
  - A Review of Quantitative Risk–Benefit Methodologies for Assessing Drug Safety and Efficacy
- IMI PROTECT: WP5
  - Review of methodologies for benefit and risk assessment of medication

Recommended for further reading:

- CIRS
  - Standardizing the Benefit-Risk Assessment of New Medicines: Practical Applications of Frameworks for the Pharmaceutical Healthcare Professional
- BSI group
  - Evaluating benefit-risk during and beyond drug development
- HTA
  - Prioritisation of health technology assessment. The PATHS model: methods and case studies

Of limited importance, requiring prior knowledge:

- FDA (requires prior knowledge)
  - A United States Regulator's Perspective on Risk-Benefit Considerations

Benefit-Risk Special Interest Group

Highlights

Group 3: Collect good case studies to share from companies and initiatives

- *Survey to EFSPI members*
- *Review of published materials*

Small survey to EFSPI members What did we ask?

- Do you have any examples from your organisation that you would be willing to share?

- Whether you have any examples within your organisation where a structured Benefit-Risk approach was used.

- If yes, please provide brief overview of the Benefit Risk methodology used. Was it a
    - Qualitative approach? e.g FDA Grid, CASS
    - Semi quantitative approach? e.g BRAT (UMBRA) framework , EMA effects table
    - Fully quantitative approach? e.g MCDA, Health Outcome Models

- At what stage of drug development was this methodology used for?
    - Pre-filing
    - Within the regulatory submission
    - In support of post-marketing updates

- Please include a short paragraph with some brief context about the project / situation.

Feedback and findings

- Most companies did not have any cases or details were still too confidential
- Three examples have been shared by AstraZeneca, Roche and GSK together with summary of wave 1 of IMI WP5.

- *All case examples seem to have used the BRAT framework*
- *Typical elements of the BRAT framework such as the Value Tree or the visual display of key R-B (Levitan 2011) were used in all cases*
- *Outcome of the BRAT framework was used for regulatory purposes by Roche (Clinical Overview)*
- *Incorporated patient perspectives to determine MAR and preference values (Roche)*
- *Future work is planned regarding assessing full quantifications beyond the visual displays (GSK, AZ, Roche) and incorporating patients perspectives (GSK)*
- *MCDA, SMAA and SBRAM methods were tested within the IMI project*

Benefit-Risk Special Interest Group

Highlights

Group 4: Working on a blueprint of the how statisticians can play a leading role in Benefit-Risk and a strategy for sharing the first 3 groups outputs

–Feedback from statistical leaders today!

–Groups 1,2 and 3 outputs will be delivered this year

–Introduction session at PSI Annual Conference-May 2013

–EFSPI/PSI One day meeting including IMI and industry case studies-September 2013

EFSPI Benefit-Risk SIG

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EFSPI Benefit-Risk SIG

Other topics from brainstorm 2012

1. Review of barriers to implementing B-R methodology

- How do we enable statisticians to support implementing B-R methodology?
- *Barriers can be split into statistical and non-statistical.*
- Non-statistical include assigning a number to clinical judgement? Are there better ways of explaining what the models are and understanding the uncertainty around the subjective assessments (potential best practice document)
- How do we best assign weights to benefits and risks-should these be assigned internally or externally (i.e. internally keeps some control, externally given some "independence" to the decision?

2. Review of the tools that are available to carry out Benefit Risk assessments

- What tools can be used – for which methods – and what are the pros/cons of each.

3. Combining types of trial data

- Is there any best practice on how to assess different types of evidence such as Randomised Clinical Trials and observational evidence

4. COMET initiative (new)

- Standardising outcome measures (e.g. which endpoints, how measured, ranges of endpoints etc)

EFSPI Benefit-Risk SIG
Next steps

- Finish off current outputs to share
  - Collection of more industry case studies
  - *Best way of sharing outputs?*
- Next tasks
  - Writing points to consider
  - Publications
    - From our outputs
    - Need unique angle
    - Brainstorm for publication plan including non-statistical audience
  - Other topics from brainstorm
    - Barriers, Tools, combining types of data, COMET
    - Which ones?
- Linking to QSPI and other initiatives

EFSPI Benefit-Risk SIG
Request to EFSPI Stats Leaders

- **We would like an interactive platform to share ideas rather than document folders on a website**
  - Is this possible via EFSPI or should we use external platforms e.g. WIKI?
  - Can we share these links via yourselves?

- **To enable greater sharing of case studies**
  - Only 3 companies and IMI shared case studies
  - Can you encourage/share anonymised case studies within your companies?

- **Suggestions for better linking with other initiatives**
  - Global sharing and alignment? Synergies?
  - COMET for standardised endpoints

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EFSPI

BACK UPS

EFSPI Benefit-Risk SIG
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   - To include examples of where statisticians can input into and lead B-R assessments
     - Such as meta analyses of internal/external data, facilitating choice of benefit/risks to use, incorporating different methodologies (including utilities and weighting)
   - Could include suggestions from a regulatory perspective
2. A set of example **case studies** (3 industry and linked to IMI case studies-continuous)
3. Links to **key publications/reviews and initiatives** and outputs from the literature (nearly complete-how frequently should we review?)
4. **Publications-** for example (to start)
   - Based on conducting interviews of experiences across companies including what has worked well, learnings and difficulties (as done for BRAT framework)
   - Based on case studies
   - Based on our outputs
5. **Technical and methodological guidance** inc software/code can be a link (to start)

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  - Different publications based on our outputs (to start)
  - Articles in newsletters, society magazines (to start)
  - Putting on sessions at conferences and one day meetings (PSI Annual Conference 2013, EFSPI/PSI One day meeting Sept 2013, *others?*)
  - Working though EFSPI statistical leaders (presenting blueprint at June 2013 meeting)
- The EFSPI website will be used as a home for both SIG information sharing but also to share more broadly -Need a better way of sharing information on EFSPI Website or via living documents