Joint EFSPI/PSI Meeting: Structured Benefit-Risk Assessment

This one-day meeting was informative, enjoyable and smoothly organised. While there is a large amount of recommended reading available online, the clear presentations, with opportunity to hear personal opinions and the subsequent discussion, rewarded any effort made to travel and dedicate the time to understand current thinking in this developing area. Breaks gave opportunity to mix with counterparts from across Europe.

Deborah Ashby (Imperial College, London), co-lead of the risk:benefit package (WP5) within IMI PROTECT, described the remit as improving the monitoring of EU medicines post-approval through the life-cycle of a drug. During the past 4 years this has focussed on methodology and communication within benefit:risk, balancing individual and population-based decision-making, incorporating perspectives of patients, prescribers, healthcare providers, regulatory agencies, and manufacturers.

A survey of available acronyms (sorry, techniques and tools) connected with risk assessment were reviewed and categorised into frameworks, metric indices, estimation techniques, and utility survey techniques. Four case studies where the benefit:risk assessment was challenging for regulators were investigated, to apply methodology as a technical exercise for illustration. In each case, four stages were completed:

1. Planning: Define purpose, context, could use BRAT or PrOACT-URL framework
2. Evidence gathering, data preparation: accept this is a complex and time-consuming stage, with mixed data formats, need for indirect comparisons. Simulations with a visualisation tool can be used to describe the situation
3. Analysis: Selection of methods, determine how far to quantify based on assumptions and stakeholder opinions, compared to a qualitative, rank-based approach
4. Exploration: Evaluate robustness of decision, implication to a risk management plan, consequences to each of patients, prescribers, healthcare providers, regulatory agencies, and manufacturers.

The communication aspect has considered the care with which clear messages need to be created, and the requirement for provision of in-depth background information to support any headlines.

A rimonabant case study (not discussed further at this meeting) report available online includes an interactive tool to adjust your own preferences. Experience has demonstrated evaluation of benefit:risk to be an iterative process, adapting as opinions are incorporated, initial assessments are reviewed, new data or approaches become available.

Andrew Thomson (MHRA) gave (his own) regulatory perspective. In summary, formalising benefit:risk gives structure to evaluations that were going on already. MHRA now create an "Effects Table" as a top-line summary. In combination with a benefit:risk assessment from an applicant, which helps MHRA understand the company's position, the areas of agreement and differences are clear which can focus discussion. Documentation of the issues also facilitates handovers between licensing and post-marketing vigilance teams within MHRA, and between rapporteur/co-rapporteur and a third country being included in the mutual recognition process for the benefit:risk assessment. There is still opportunity to improve the understanding of benefit:risk across the group of regulatory agencies. Further motivation for benefit:risk comes from pharmacovigilance legislation requiring thorough PSUR updates with a new risk evaluation for licensed products.

Andrew described the example of Xeljanz, particularly interesting as FDA and MHRA assessments gave differing opinions. The review considered different lines of therapy, combination therapies, and doses, after which FDA granted approval for one dose as second-line therapy, while CHMP refused approval for 3rd line. It was emphasised that

MHRA took no account of the oral administration aspect in their review (existing treatment options are infusions).

Rebecca Sudlow (Roche Products Limited) gave her company perspective on implementing structured benefit:risk. It has taken dedicated resource to achieve adoption, but Roche have successfully built a framework, toolkit, guidance that expects teams to document their plans, reasoning, qualitative and quantitative assessments throughout the life of a clinical development programme. The result is an opportunity to move from the traditional reporting summary (Table 1: Impressive efficacy, Table 27 onwards: Safety tables, Conclusion: effective with an acceptable safety profile) to a more integrated approach.

Richard Nixon (Novartis), Ian Hirsch (AstraZeneca), Christine Hallgreen (Imperial College) and Alfons Lieftucht (GSK) each gave case study experience, Richard and Christine using IMI PROTECT examples (natalizumab and telithromycin respectively), and Ian and Alfons internal company examples. Richard illustrated the concept of applying subjective weightings to a single quantity of benefit:risk using the scoring system for the heptathlon: each activity is different with a different scale, how much “improvement” in each is equivalent for comparison? The natalizumab example had a very rare but very serious side effect, and adjustments in weighting for the adverse event compared to those for beneficial variables could be made to identify a tipping point. Common themes were how to source justifiable weights for the model components, how to incorporate the correlations between the efficacy and safety variables being included, and whether a by-patient utility-type quantity across efficacy and safety would be an alternative approach. The presenters were keen to share their progress so far, and support others as they attempt to roll out similar approaches in their organisations, to avoid inefficiencies creating multiple versions of the same guidance documents.

I strongly recommend the IMI PROTECT website with its vast resource of material, including a methodology review and case study reports. I also heartily recommend attending PSI events that match your areas of interest, this was my first for quite a while and it was extremely worthwhile.

Ann Smith (AstraZeneca)