Implementing a structured BR approach – A company perspective

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- George Quartey (Stats Methodology and Research Group)
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Presentation Outline

- What were the opportunities/areas for improvement in BR assessment?
- Challenges to embed a new way of thinking/working
- Which approach/method is appropriate?
- How to incorporate CBR thinking into the Roche development process?
- Experiences so far
- Barriers to implementation / Increasing chances of success

Opportunities for improvement

Table 1 Percentage of Patients with an ACR20, ACR50, and ACR70 Response at Week 24: DMARD-Inadequate Responders: 6-Month Pooled Data (ITT Population)

Parameter	Placebo + DMARD (N=1010)	TCZ 4 mg/kg + MTX (N=612)	TCZ 8 mg/kg + MTX (N=1406)
ACR20	25.8%	49.7%	59.2%
ACR50	9.6%	27.3%	37.0%
ACR70	2.4%	11.4%	18.5%

MTX=methotrexate; TCZ=tocilizumab
All tocilizumab treatment groups were statistically superior to placebo at $p < 0.0001$
Tocilizumab 8 mg/kg was statistically superior to 4 mg/kg at $p < 0.05$

Table 2…

Table 27…

Table 28 Serious Adverse Events Reported by ≥ 2 Patients Receiving Tocilizumab in the Double-Blind Studies

	TCZ 8 mg/kg N = 288	MTX N = 284	TCZ 4 mg/kg + DMARD N = 774	TCZ 8 mg/kg + DMARD N = 1582	Placebo + DMARD N = 1170
Preferred term	N (%)	N (%)	N (%)	N (%)	N (%)
Infections					
Pneumonia	2 (0.7)	2 (0.7)	6 (0.8)	9 (0.6)	4 (0.3)
Cellulitis	-	-	-	9 (0.6)	1 (0.1)
Herpes Zoster	-	-	-	5 (0.3)	-
Urinary tract infection	-	-	1 (0.1)	1 (0.1)	4 (0.3)
Sepsis	-	1 (0.3)	2 (0.3)	1 (0.1)	1 (0.1)
Gastroenteritis	-	-	3 (0.4)	-	-
Bronchitis	-	-	1 (0.1)	1 (0.1)	1(0.1)
Gastrointestinal					
Diverticular perforation	-	-	-	2 (0.2)	-
Gastric Ulcer	1 (0.3)	-	-	1 (0.1)	-
Esophagitis	-	-	1 (0.1)	1 (0.1)	-
Cardiac					
Acute coronary	-	-	-	2 (0.1)	3 (0.3)

Impetus for changing cBR: ex- Actemra briefing document, FDA Adv. Comm. (29-Jul-2008)

BR Statement (2008)

"In summary, the benefits of tocilizumab therapy in earlier stage RA and inadequate responders to DMARDs and to anti-TNF agents has been demonstrated.

"The overall benefit/risk assessment of tocilizumab in patients with RA is favorable. Tocilizumab provides a new therapeutic option for patients…"

Opportunities for improvement in BR assessment

- Integrated rather than separate presentation of key efficacy and safety data.
- Display of comparative effects
- Translation of observed treatment effects into clinical terms?
- Clear rationale behind why observed efficacy offsets harms

Internal drivers...

Feeling that B-R assessments seemed to be somewhat inadequate

Evaluate B-R profile to enable *decision making* at key points during product development

Facilitate an understanding of the *clinical value* of a specific molecule

External drivers…

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

31 August 2011
EMA/718294/2011
Human Medicines Development and Evaluation

Benefit-risk methodology project

Work package 3 report: Field tests

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

April 2012
EMA/CHMP/ICH/544553/1998
Committee for medicinal products for human use (CHMP)

ICH guideline E2C (R2)
Periodic benefit-risk evaluation report (PBRER)

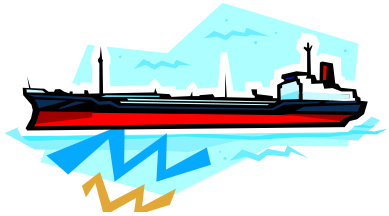
Roche

FDA B-R Assessment: Jakafi approval

Benefit-Risk Assessment Framework

Decision Factor	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition: MF		MF is a serious, life-threatening condition in which death is due to evolution into AML (12%), bleeding (11%), portal hypertension (7%), and liver insufficiency (9%).
Clinical Manifestations	Splenomegaly and symptoms which disrupt quality of life	
Median Survival (all groups)	57 months	
Survival high risk	27 months	
Survival intermediate-2	48 months	
Approved available therapy	No approved therapy	
Unmet Medical Need: Therapy: Off label use of interferon-alpha, anagrelide, dexamethasone, hydroxyurea, erythropoietin, thalidomide, splenic radiation, and allografts.	Allograft is the only curative therapy (7-year survival is 60%). Only a fraction of patients with MF are eligible. All other therapies are palliative and have significant side effects.	For most patients, there is no curative therapy, and no effective treatment which reduces symptoms and splenomegaly for a long time. There is an unmet medical need in MF.
Clinical Benefit: 2 randomized, well controlled trials were conducted with reproducible results.	42% and 29% of ruxolitinib treated patients in the two trials displayed ≥35% reduction of splenic volume. In the pivotal phase III trial, 46% of patients experienced ≥50% reduction in total symptom score. Long term benefit and toxicity unknown.	Two large well controlled and well designed trials met efficacy endpoints when measured at 24 and 48 weeks of therapy. Uncertain is the how long benefits will last beyond the 24 and 48 weeks and what will be the toxicity of long-term treatment.
Risks:	Ruxolitinib Arms	Thrombocytopenia was successfully managed by a dose adjustment schedule. Anemia was managed by RBC transfusions. The risks of long term therapy have not been characterized.
Early deaths (≤28 days)	Not increased	
SAEs	Not increased	
AEs		
↓platelets (Grade 3)	Increased	
↓platelets (no Grade 4)	Not increased	
Bleeding	Not increased	
Anemia (Grade 3)	Increased	
Anemia (Grade 4)	Increased	
Infections	Not increased	
AEs leading to discontinuation	Not increased	
AEs leading to dose reduction	Increased	
Risk Management: Need of studies for toxicity of long-term therapy.	Two phase III trials showed significant benefit and minimal risks for up to 48 weeks of treatment. Need PMC for longer term follow-up of response duration and toxicity.	PMR for follow-up (for 3 years after randomization) of phase III trial populations for myelosuppression PMC for post-marketing follow-up of efficacy and safety outcomes of current randomized trials and to report on discontinuation of at least 150 patients previously entered onto the randomized trials to determine if specific cautions are appropriate to describe discontinuation strategies.

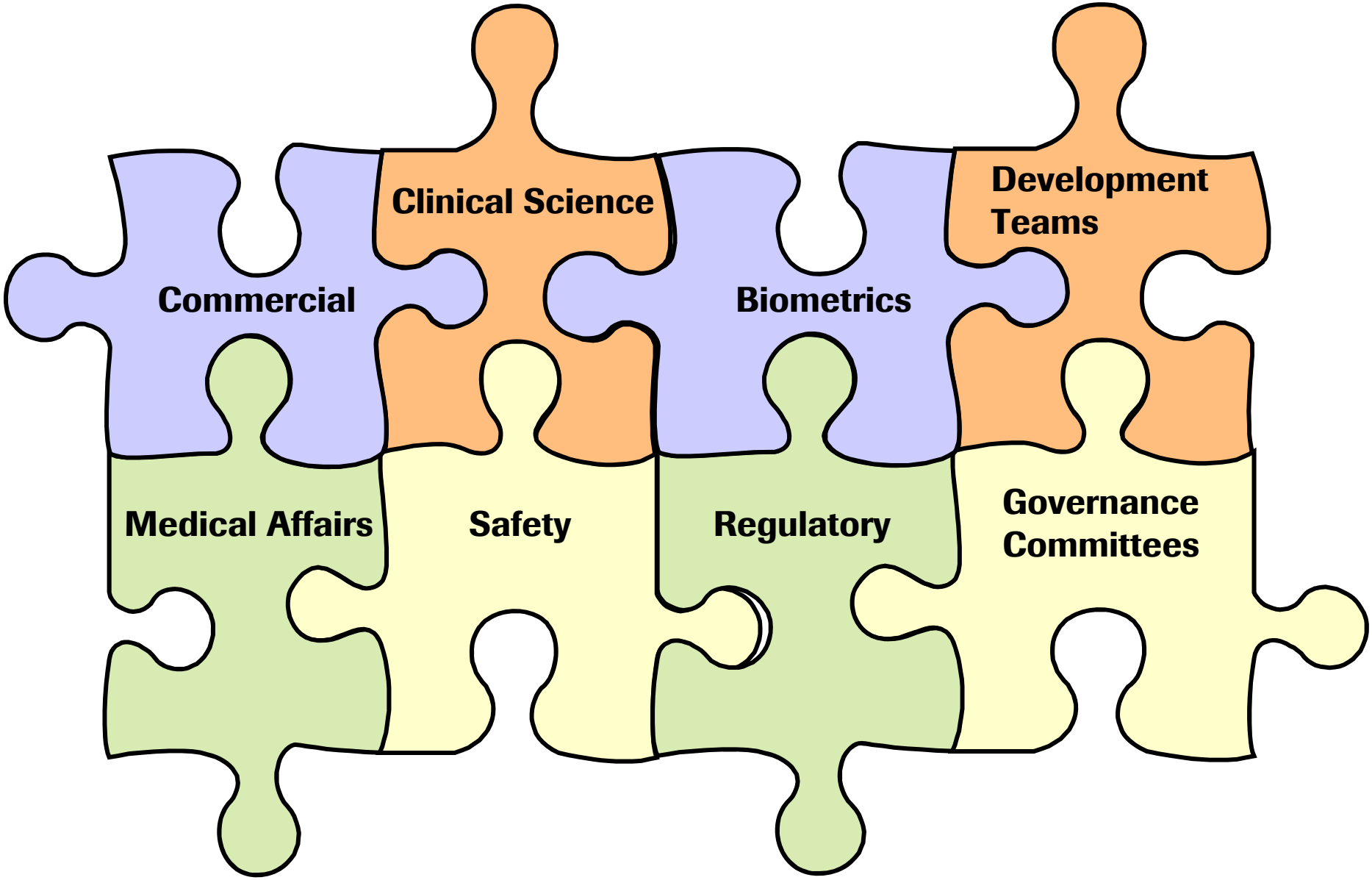
Challenges to embed a new way of thinking/working



- Like steering an oil tanker …..
- Complexity of organisation
  - Many functions
  - Many sites around the world
  - Disease area silos
- Too much choice in methods
- Change fatigue (post merger)

Champion needed

Key Partnerships within the company



I) Which approach/method is appropriate?

Wanted an approach that:

- is systematic, descriptive and incorporates quantitative models as needed
- provides the outcome in an easily understandable format such as charts, plots (data visualisation)
- is flexible and adaptable to different situations
- is able to use all available data (pre- and post-market)
- has clear data collection methods
- incorporates stakeholder perspectives (patient, physician)
- accounts for uncertainties in B-R estimates

II) Which approach/method is appropriate ?

- Decision to focus on a subset of tools and methodologies
- Toolkit developed focusing on
  - a descriptive framework for conducting a CBR assessment
  - 3 potentially useful quantitative methods that complement the framework
- Decision to focus on CBR assessment at time of filing
- Process / methodology toolkit updated to incorporate PBRER requirements

III) Which approach/method is appropriate?

Frameworks selected by Roche:

- BRAT
- PrOACT-URL
- FDA Benefit Risk Framework

Additional quantitative methods to complement the framework were:

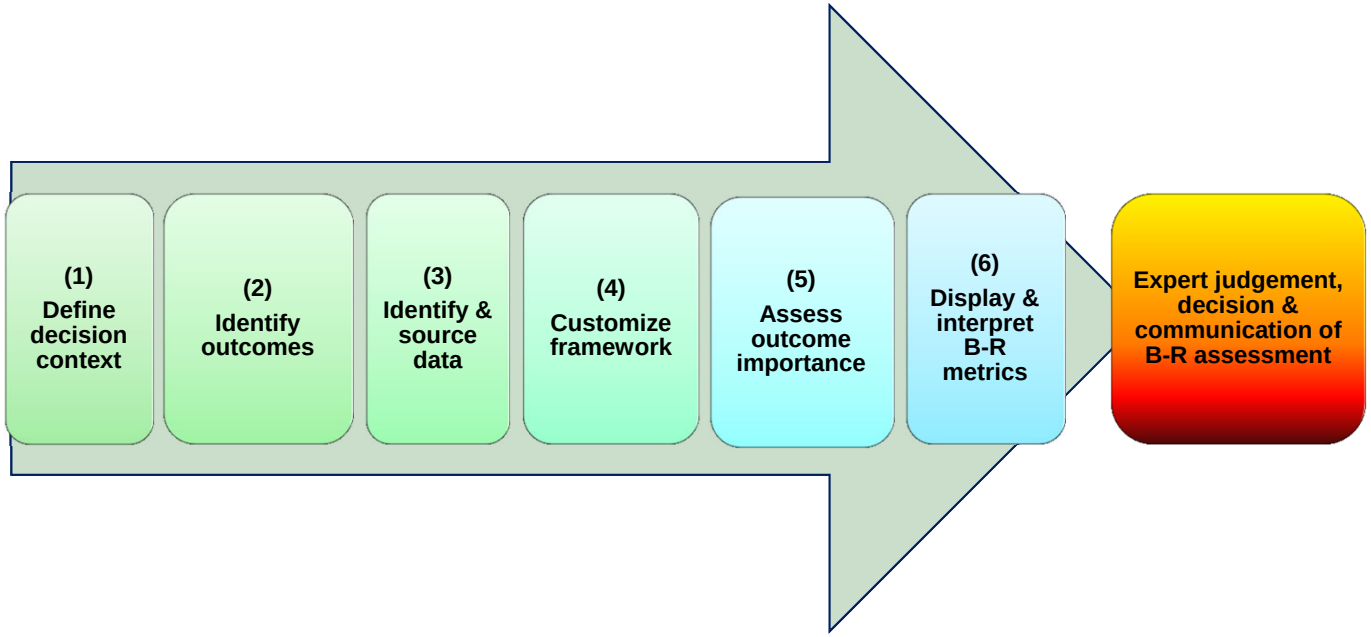
- MCDA
- Q-TWIST
- Conjoint Analysis

BRAT framework for descriptive assessment

Built on a number of principles

- **Transparency** – systematically document what is included and what is excluded. Consistency of approach across project teams.
- **Documentation of reasoning** behind electing to leave out a particular set of benefit or risk outcomes in an assessment
- Tabular output of parameters and results are **easily interpretable** by readers
- **Visualisation** of data

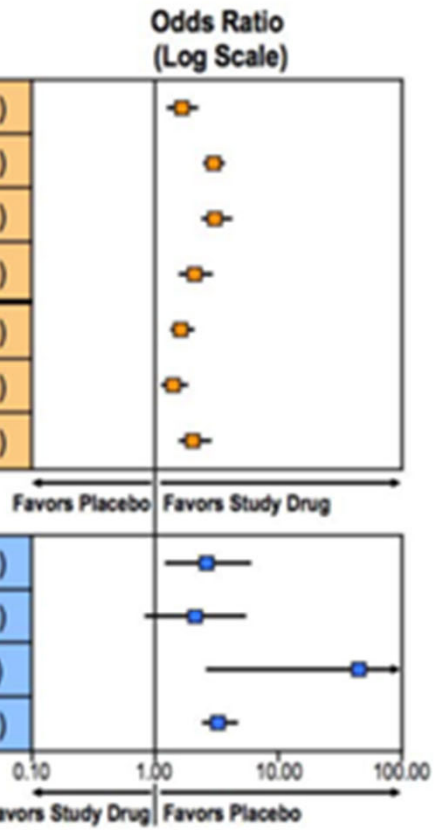
BRAT framework for descriptive assessment



BRAT=Benefit Risk Action Team

Example product of a BRAT framework approach

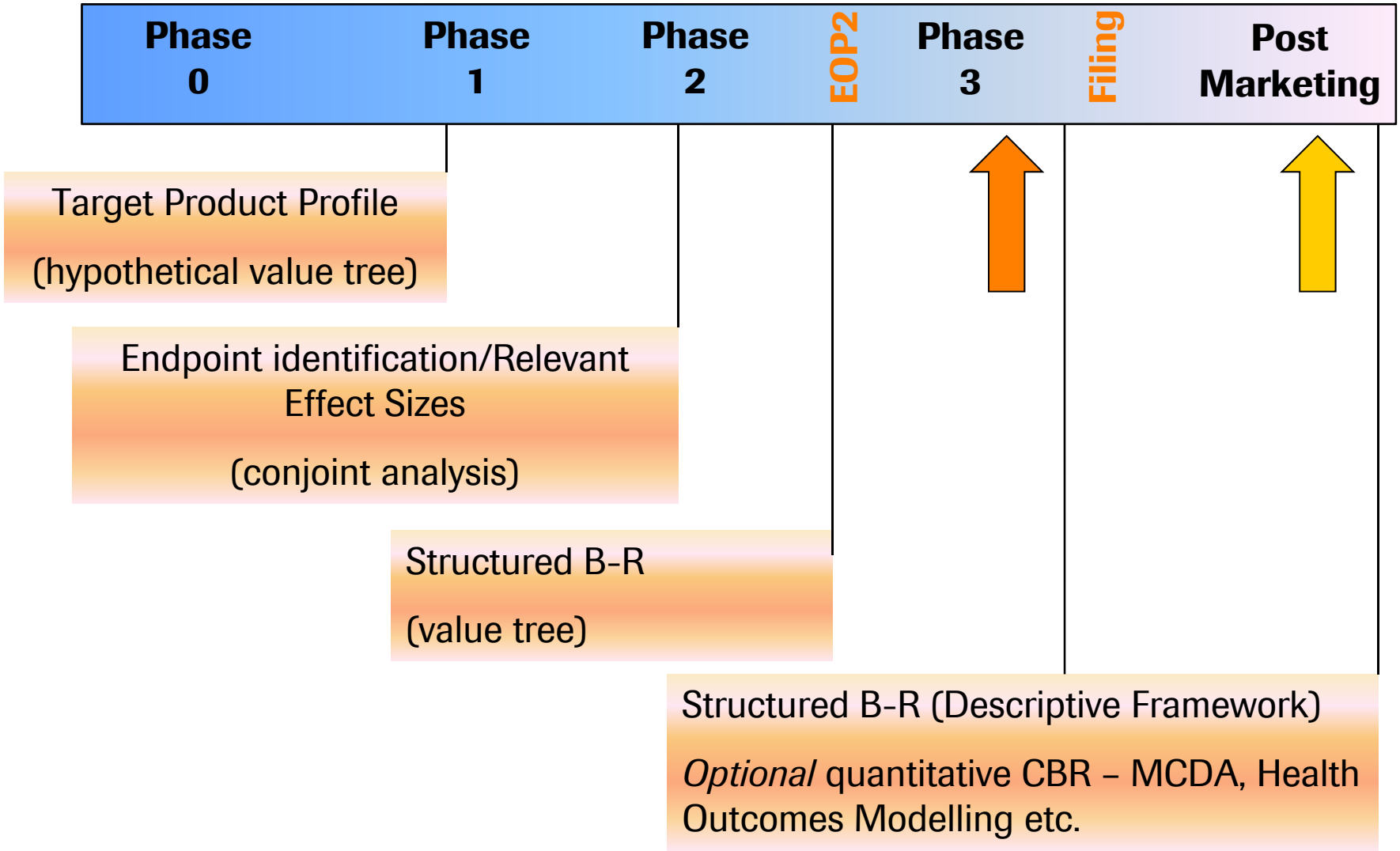
		Outcome	Study Drug (%)	Placebo (%)	Odds Ratio (95% CI)
Benefits	Pain Reduction	Rapid onset	34.6	24.9	1.60 (1.27, 2.00)
		Headache relief	59.2	33.5	2.89 (2.43, 3.44)
		Pain-free response	28.4	11.8	2.97 (2.31, 3.83)
		Sustained response	45.2	28.7	2.05 (1.54, 2.72)
	Other	Reduced sensitivity to sound and light	64.1	52.8	1.59 (1.32, 1.92)
		Reduction in nausea or vomiting	73.9	67.4	1.37 (1.08, 1.72)
		Reduction in functional disability	48.4	32.0	2.00 (1.51, 2.64)
Risks	Individual Risks	Transient triptan sensations	3.5	1.4	2.53 (1.20, 5.34)
		Central nervous system AEs	3.4	1.7	2.07 (0.83, 5.12)
		"Chest-related" AEs	11.7	0.3	42.6 (2.55, 710)
		Triptan-related Adverse Event	21.2	7.8	3.17 (2.34, 4.29)



Favors study drug

Favors placebo

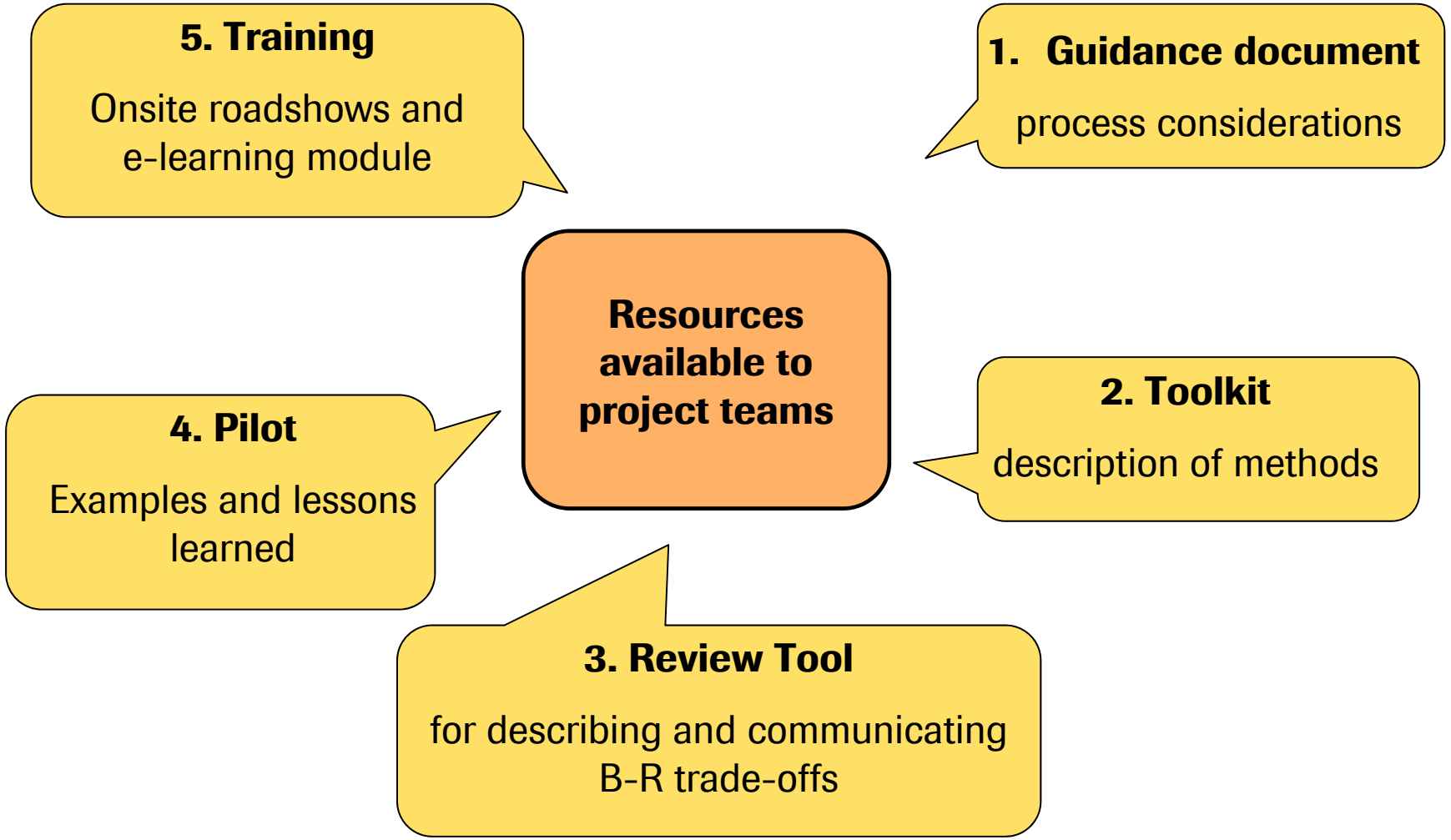
When can we incorporate structured B-R info development?



Who does the assessment?

- The Project Team Leader is accountable for carrying out the necessary activities within the team
- Teams are required to:
  - ➢ Develop a strategy for describing the B-R profile
  - ➢ Create a plan for assessing the B-R profile
  - ➢ Document the B-R assessment rationale, outcome, etc.
- Clinical Science Leader organizes and leads the B-R sub-team:
  - Safety Scientist
  - Regulatory
  - Biostatistician

How do we help encourage change?



Experiences so far

Methodology	Situation
BRAT framework	sNDA – presented in the clinical overview, based on pooled data PBRER – individual studies presented (1 per indication)
“value tree” from BRAT + FDA Grid	PBRER in a mature product (mix of clinical trial data and post marketing safety data)
PrOACT-URL	PBRER in a mature product
Conjoint Analysis	New disease area with no defined regulatory pathway What endpoints are important to the patient? What endpoints are important to the physician
MCDA	Internal pilots only

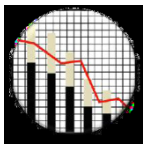
…implementing a structured B-R is easier said than done …

Reluctance to change (“not in my backyard”)

Lack of alignment / buy-in across agencies and stakeholders

Lack of expertise to implement concept

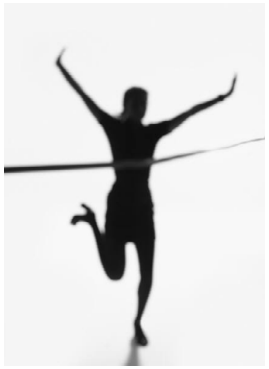
Lack of resources to implement models



No consensus about the scope of the applicability of frameworks

Successful implementation of a structured B-R assessment framework requires….

- Awareness of barriers for change and possible solutions
- Effective change management through awareness of need for framework
- Support from senior management
- Availability of talent / expertise to execute framework
- Consensus on the best approach
- Use of pilots with Roche data / first hand experience
- Training of staff
- Time



How have other companies done this?

- Are there any lessons that we can all learn from your experiences?

Doing now what patients need next