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Patient and Public Involvement in Regulatory Decision-Making

Kimberley Hockley

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IMI-PROTECT

Pharmacoepidemiological Research on Outcomes of Therapeutics by a European ConsorTium

The overall objective of PROTECT is to strengthen the monitoring of the benefit-risk of medicines.

Work Package 5:

- Develop methods for continuous benefit-risk monitoring of medicines, by **integrating data on benefits and risks** from clinical trials, observational studies and spontaneous reports

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Patient and Public Involvement

Patient and public:

Clinical trial participants, patients and potential patients, disabled people, parents and guardians, people who use health and/or social care services, carers, members of the public, and the organisations who represent the interests of these consumers.

Involvement:

An active partnership between stakeholders in the research process, rather than the use of people as ‘subjects’ of research. Public involvement in research is often defined as doing research ‘with’ or ‘by’ the public, rather than ‘to’, ‘about’ or ‘for’ them.

Evidence Based Medicine

"EBM is the conscientious explicit, and judicious use of current best evidence in **making decisions** about the care of individual patients" taking into account "**individual patients predicaments, rights and preferences** using best evidence from clinically relevant research."

Sackett et al, 1996

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Regulatory decision-making: the licensing challenge

- The task of regulators (EMA, FDA etc) is to make good and defensible decisions regarding which medicines should receive a license for specific indications, based on the available evidence of risks and benefits
- It is increasingly important to be able to justify and explain these decisions to patients and other stakeholders.
- Can more formal approaches of decision-making help regulators do this better?

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Aim

To test and evaluate formal methods of decision-making that can be used to justify and explain regulatory decisions to patients and public.

Descriptive framework:

Pharmaceutical Research and Manufacturers of America (PhRMA) Benefit-Risk Action Team (BRAT) framework

Case study: Raptiva (efalizumab)

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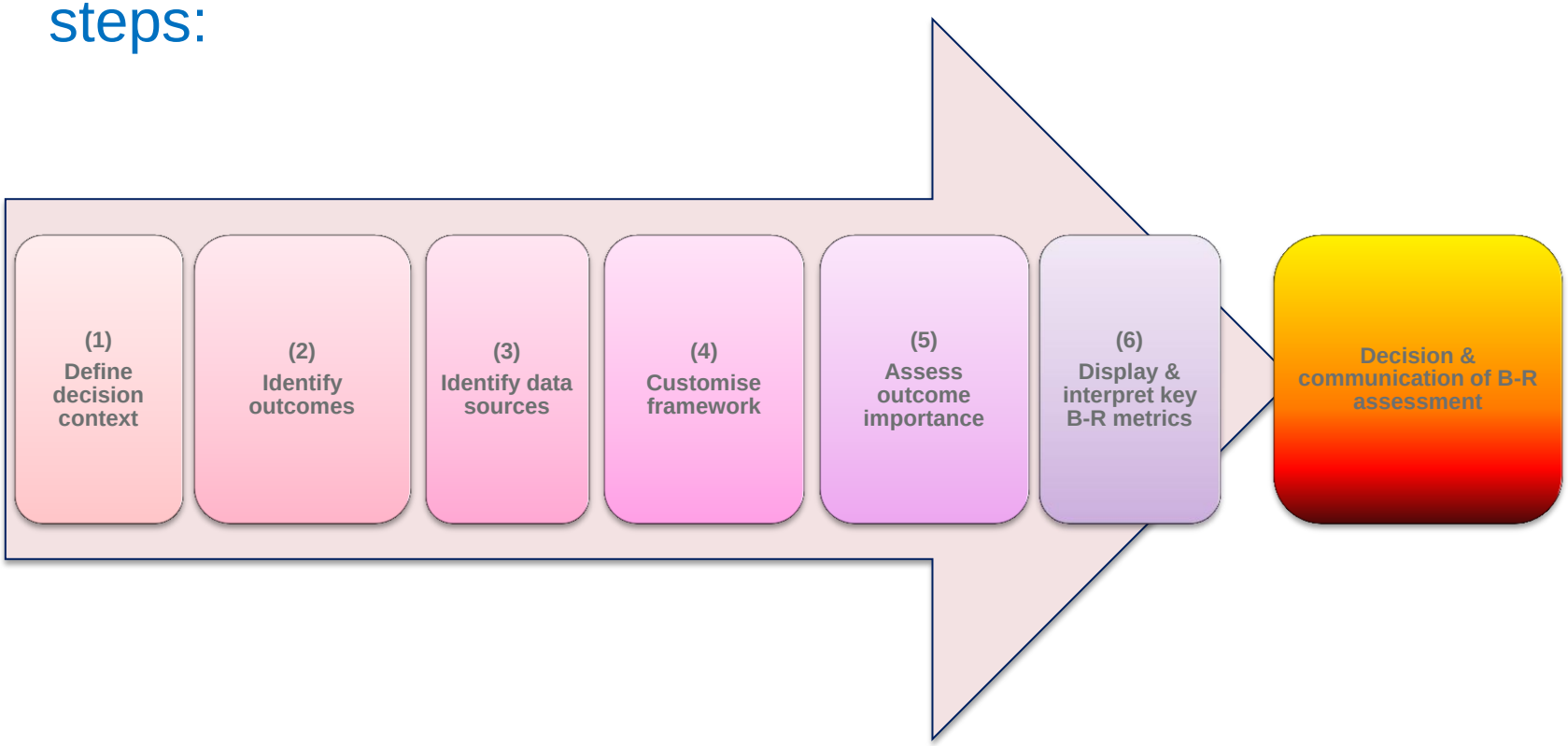
BRAT

Divides decision making process in the following 6 steps:



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Step 1: Decision Context

Indication	Raptiva is indicated in the treatment of “high need” adult patients with moderate to severe chronic plaque psoriasis
Drug	Raptiva (efalizumab) is a recombinant, humanized IgG1 monoclonal antibody that targets CD11a
Formulation/Dose	An initial single dose of 0.7 mg/kg body weight is given followed by weekly injections of 1.0 mg/kg body weight, subcutaneously
Comparator	Placebo
Population	“High need” adult patients with moderate to severe chronic plaque psoriasis who have failed to respond to, or who have a contraindication to, or are intolerant to other systemic therapies
Time Frame for Outcomes	12 weeks for PASI 75 (efficacy/favourable effects), 3 years for PML
Perspective	Regulator (at EMA)

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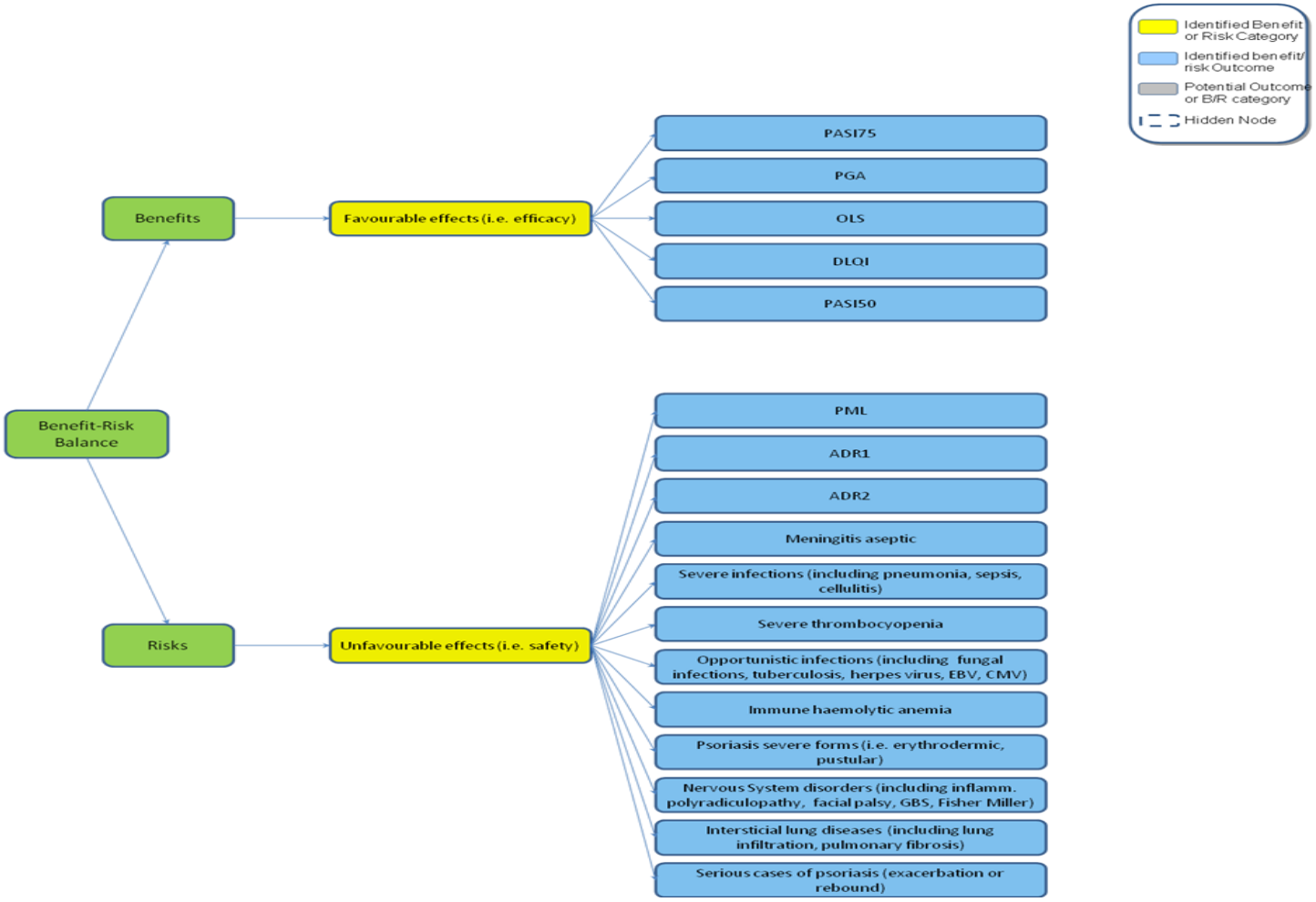
Step 2: Identify and select benefit and risk outcomes and associated measures



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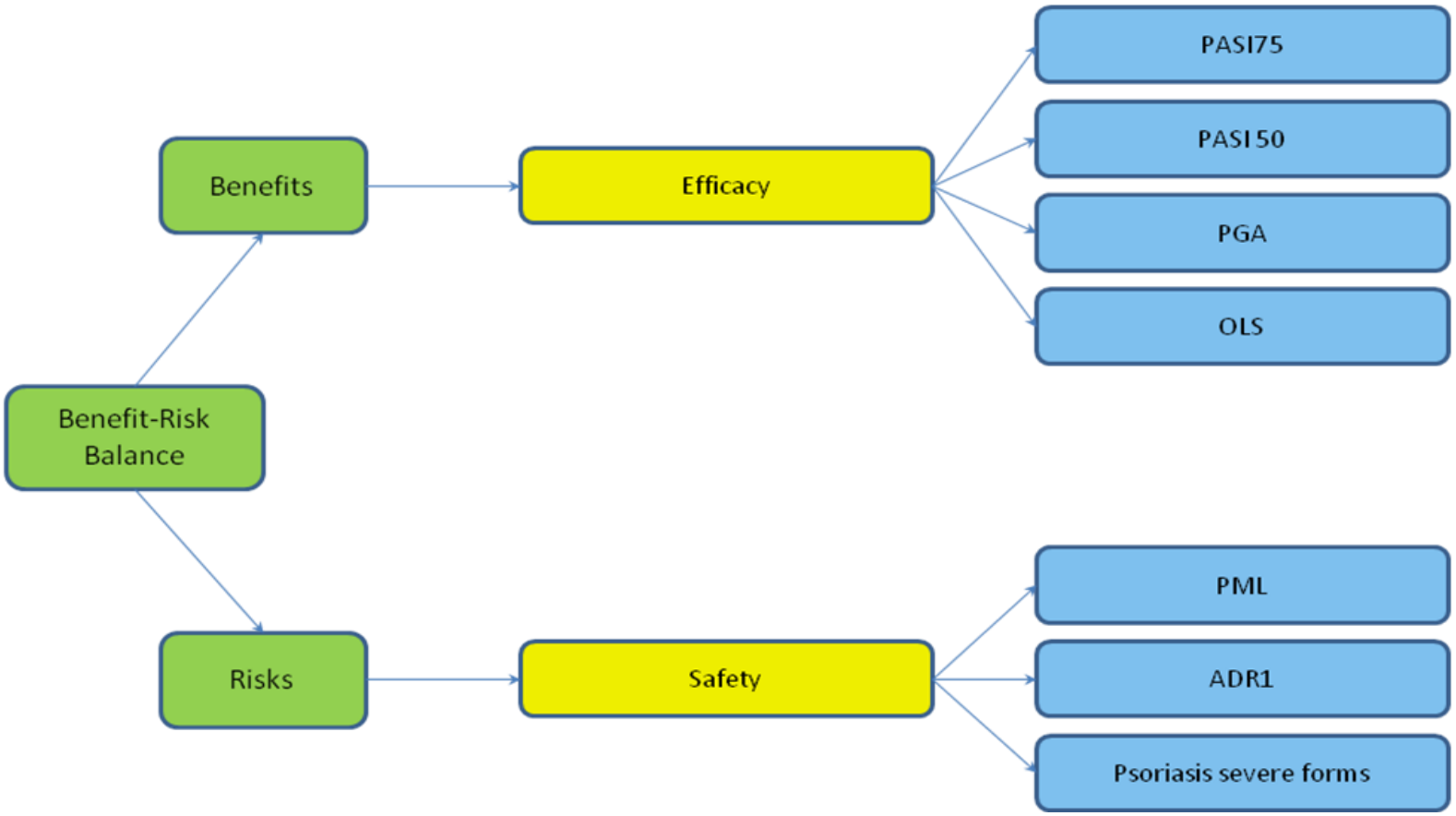
Step 3: Identify and extract data sources

Measure	Source	Inclusion	Rationale
PASI75	Clinical trials	Yes	Complete data
PGA	Clinical trials	Yes	Complete data
OLS	Clinical trials	Yes	Complete data
DLQI	Clinical trials	No	Average and standard deviation missing
PASI 50	Clinical trials	Yes	Complete data
ADR1	ISS	Yes	Complete data
ADR2	ISS	No	Percentage of events in placebo group not given; percentage of events for Raptiva not precise (range given)
Meningitis aseptic	PSUR10	No	Background epidemiology not known
Serious infections including pneumonia, sepsis, cellulitis	ISS	Yes	Complete data
Opportunistic infections including fungal infections, tuberculosis, herpes virus infections, EBV, CMV	PSUR10	No	RMP only states background epidemiology of tuberculosis; background epidemiology of other conditions not known

Step 4: Customise framework



Step 5: Assess outcome importance

Outcomes are assessed for their importance to decision-makers and other stakeholders, and the subsequent rankings and weightings are applied to the tree.

BRAT framework does not advocate a specific method to weigh the preferences of outcomes in the value tree.

Use of multi-criteria decision analysis (MCDA)

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Step 6: Display and interpret key benefit-risk metrics

Key benefit-risk summary table

		Outcome	RAPTIVA Risk / 1000 pts	Placebo Risk / 1000 pts	Risk Difference (95% CI)/ 1000 pts		Relative Risk (95% CI)	
Benefits	Efficacy	PASI75	280	36	244	(151, 362)	7.819	(4.999, 12.380)
		PASI 50	567	200	360	(303, 431)	2.800	(2.210, 3.650)
		PGA	305	52	251	(141, 396)	5.778	(3.602, 9.337)
		OLS	292	37	254	(145, 392)	7.813	(4.731, 13.270)
Risks	Safety	PML	0	0	0	(0, 0)	18.400	(5.400, 45.960)
		ADR1	410	240	170	(130, 210)	1.710	(1.510, 1.940)
		Psoriasis severe forms	33	15	17	(6, 29)	2.170	(1.270, 3.970)

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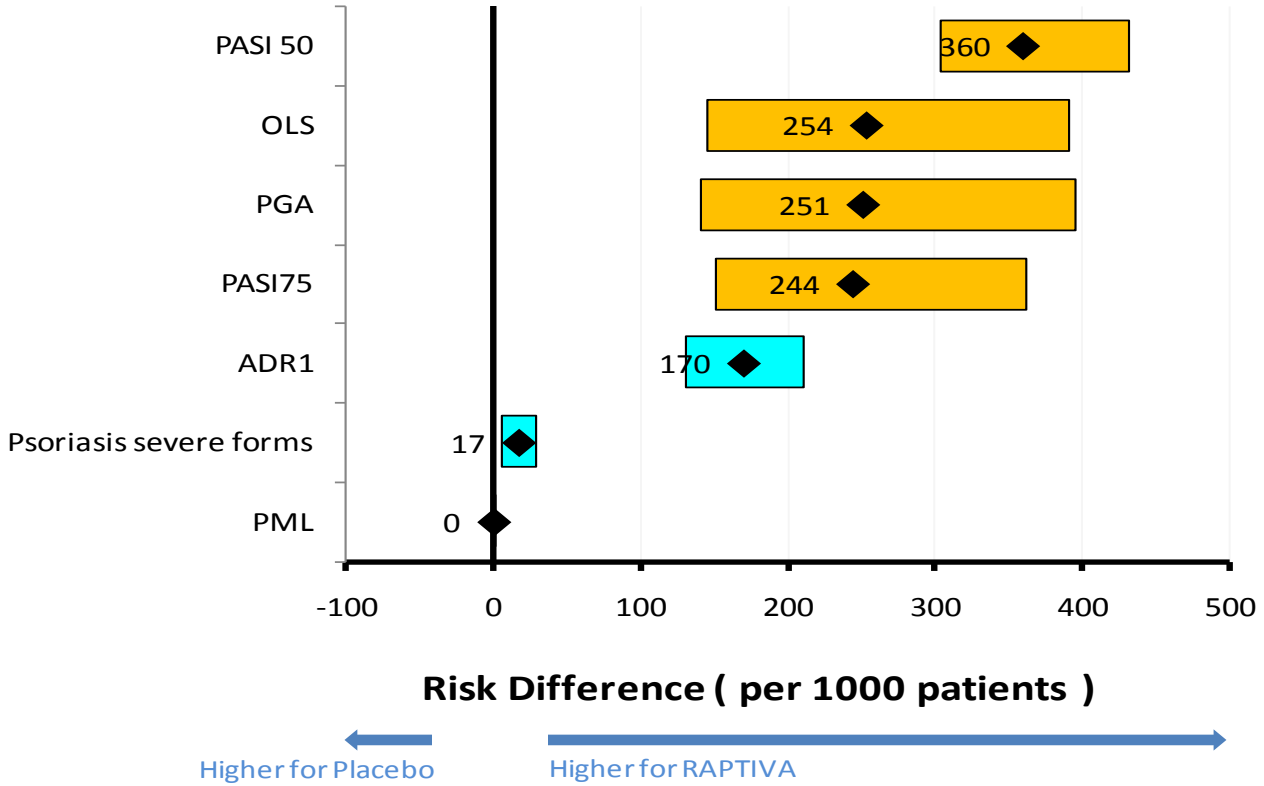
Step 6: Display and interpret key benefit-risk metrics

Forest plot: Risk difference for key favorable and unfavorable effects (Raptiva compared to placebo)



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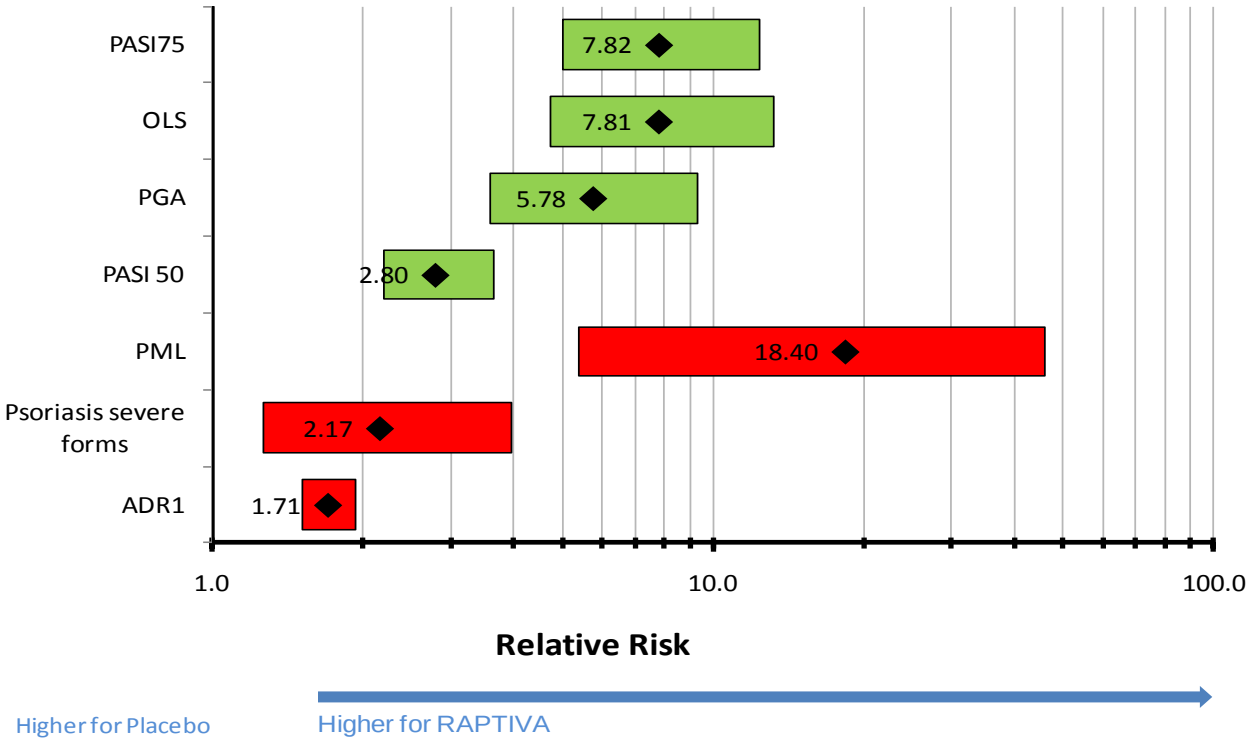
Step 6: Display and interpret key benefit-risk metrics

Forest plot: Relative Risk for key favorable and unfavorable effects (Raptiva compared to placebo)



Discussion

- Easily communicable, highly transparent
  - Provides insight by providing a strong context to decision-making
- Framework can apply to any stage of a product lifecycle
  - I.e. early development to post-marketing

Discussion

- Various data sources of differing quality
  - Clinical trials
  - Epidemiological studies
  - Spontaneous reports

- Framework is only possible when data for a comparator such as placebo, background epidemiological rates, or active comparator is available

Further Work

From an ethical and moral perspective, the values and preferences of patients should be included in regulatory decision-making:

- »Who can be involved?
- »How can they be involved?

Methods of preference elicitation:

- Multi-criteria decision analysis
- Nominal group techniques
- Discrete choice experiments

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'The processes described and conclusions drawn from the work presented herein relate solely to the testing of methodologies and representations for the evaluation of benefit and risk of medicines. This report neither replaces nor is intended to replace or comment on any regulatory decisions made by national regulatory agencies, nor the European Medicines Agency.'

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Questions