If You Are Serious About Benefit:Risk Assessment

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Basic & Well-Accepted Facts

- All pharmaceutical products have side effects (risk).
- Risk associated with a product should be evaluated with respect to its achievable benefit and the underlying disease.
- Benefit/risk assessment is an ongoing process. While benefit can be experienced earlier, risk could surface later.
- Much work has been dedicated to this subject; challenges abound.
- Benefit/risk assessment cannot replace rigorous assessment of efficacy and safety.

Outline

- Benefit:risk metrics
  - Benefit risk ratio
  - Combining multiple outcomes
  - Patient level measure
  - Classifying benefit and risk into a multinomial outcome
- PhRMA Benefit Risk Action Team
- Who makes benefit:risk decision?
- Summary

Benefit Risk Ratio: The modern version

- Compare two treatments A and B where A is more efficacious (on a binary endpoint) but has more risk (measured by a binary endpoint).
- NNTB – Number needed to treat (NNT) so that one more patient benefits with A than with B
  - $NNTB = 1/(pe_A - pe_B)$
- NNTH – Number needed to treat so that one more patient experiences the risk with A than with B
  - $NNTH = 1/(pr_A - pr_B)$
- $NNTH / NNTB = (pe_A - pe_B)/(pr_A - pr_B)$

Prasugrel For Reduction of Cardiovascular Events in Patients with Acute Coronary Syndrome (ACS)

Cardiovascular and Renal Drugs Advisory Committee
Silver Spring, Maryland
February 3, 2009

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Prasugrel: Evidence of Effectiveness (1)

- Phase 3, multinational, randomized, double-blind, active-controlled study.
- Subjects with acute coronary syndrome (ACS), scheduled to undergo percutaneous coronary intervention (PCI).
- Randomized 1:1 to oral prasugrel (60-mg load; 10-mg daily maintenance) or clopidogrel (300-mg load; 75 mg daily maintenance).
- Hypothesis: prasugrel plus aspirin is superior to clopidogrel plus aspirin in reducing cardiovascular events.

Source: FDA Advisory Committee website.

Prasugrel: Evidence of Effectiveness (2)

- 717 principle investigators, 725 study centers, 13,608 subjects enrolled.
- Randomization stratified by presentation
  - Unstable angina or non-ST-segment elevation myocardial infarction (UA/NSTEMI)
  - ST-segment elevation MI (STEMI)
- Composite endpoint
  - Cardiovascular death
  - Nonfatal myocardial infarction
  - Nonfatal stroke
- Median follow-up=15 months (mean=12 months)

Prasugrel: Major Efficacy Findings

- Statistically significant reduction in composite endpoint in the prasugrel group (19% reduction in relative risk with P-value = 0.002; 2% reduction in absolute risk).
- Superiority efficacy driven by non-fatal MI, positive trend on cardiovascular death, neutral on stroke.
- Persuasive efficacy results across UA/NSTEMI, STEMI, and overall ACS populations.

  However, there were more deaths and bleeding episodes in the prasugrel group.

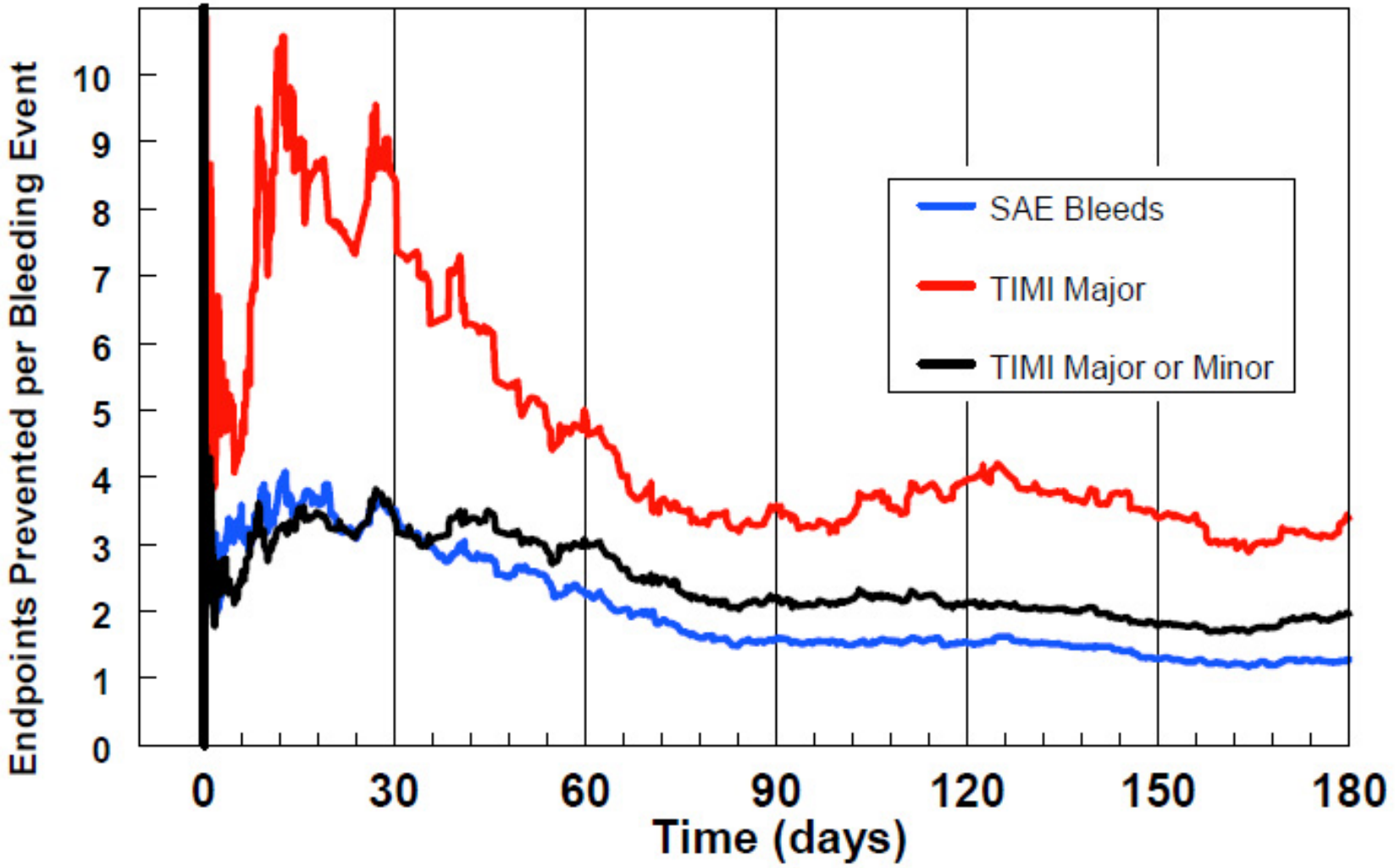
Bleeding Definition

- TIMI Trial defined “Major Bleeding” as any intracranial hemorrhage, or overt bleeding requiring intervention associated with a decrease in hemoglobin ≥ 5 g/dL.
- TIMI Trial defined “Minor Bleeding” as clinically overt bleeding associated with a decrease in hemoglobin of ≥ 3 g/dL but < 5 g/dL.
- Bleeding was categorized as related to, or not related to, coronary artery bypass graft (CABG) surgery.

Adjudicated Bleeding by TIMI Classification

TIMI Bleeding	Prasugrel			Clopidogrel			HR (95% C.I.)
Non-CABG-Related:	N	n	%	N	n	%	
Fatal	6741	21	0.3	6716	5	0.1	4.19 (1.58, 11.1)
Life-threatening	6741	85	1.3	6716	56	0.8	1.52 (1.08, 2.13)
Major	6741	146	2.2	6716	111	1.7	1.32 (1.03, 1.68)
Minor	6741	164	2.4	6716	125	1.9	1.31 (1.04, 1.66)
Minimal	6741	460	6.8	6716	314	4.7	1.47 (1.28, 1.70)
CABG-Related:							
Fatal	213	2	0.9	224	0	0.0	
Major	213	24	11.3	224	8	3.6	3.50 (1.53, 7.99)
*All Fatal:	6954	23	0.3	6940	5	0.1	4.59 (1.75, 12.1)

Cumulative Benefit-Risk of Prasugrel Compared to Clopidogrel by Time: All ACS Population



Dealing with Multiple Outcomes

- Women's Health Initiative (WHI), a 15-year project sponsored by the NIH in the US, involved over 161,000 postmenopausal women aged between 50 and 79.
- Focused on strategies for preventing heart disease, breast and colorectal cancer, and osteoporosis.
  - Randomized clinical trials, enrolling > 68,000 women
    - Hormone Replacement Therapy (HRT)
    - Dietary Modification
    - Calcium/Vitamin D
  - The Observational Study (OS), enrolling > 93,000 women
  - Community Prevention Study
- Enrollment started in Sept 1993 and completed in July (RCT) and Dec1998 (OS)

HRT Component of the WHI

- Group Seq design with 2 interim looks and OB boundary. The primary endpoint: the number of women who died of coronary causes or had a nonfatal myocardial infarction.
- Freedman et al (1996, *Controlled Clin Trials*) argue that a single outcome is not appropriate for prevention trial since the preventions might have effects on several diseases. They propose combined indices.
  - Unweighted combined index
    - $U = d_1 + d_2 + \ldots + d_k$
  - Weighted combined index
    - $W = w_1 d_1 + w_2 d_2 + \ldots + w_k d_k$

  d_i is the observed difference in proportions for outcome i.

Proposed Weights for the HRT

Diseases	HRT	Dietary	Calcium/ Vitamin D
CHD Incidence	0.50	0.50	
Breast Cancer	0.35	0.35	
Colorectal or Endometrial Cancer	0.15 (endometrial)	0.50 (colorectal)	0.50 (colorectal)
Hip Fracture	0.18		0.18
Death (Others)	1.00	1.00	1.00

Patient Level Measure

- Trade-off at the individual patient level
  - Patient global assessment –patients rate their overall experience (perceived benefit and risk) using an ordinal response.
  - For medications used to relieve signs and symptoms.
  - Potential problem - Patients tend to equate risk with untoward symptoms and may not know the *silent* risk suggested by abnormalities in lab parameters.

The Discounting Approach

- Overarching concept: the original benefit measure is discounted for the presence of untoward safety experience according to some predetermined rules.
- TWiST: Time without symptoms of disease and toxic effects (Ref: Gelber et al (1989), Biometrics)
- Q-TWiST: Quality-adjusted TWiST (Ref: Glasziou et al (1990) Stat in Medicine)
- Quality-adjusted life years gained has been used in Health Technology Assessment.

Discounting at Patient Level

- Consolidate safety data by MedDRA system organ class (SOC).
- Score the safety experience by taking into account the seriousness, severity, and frequency of adverse experience in various SOCs.
- Discount the efficacy by the adverse experience summarized in the safety score.

  benefit-less-risk = benefit – f · (safety score)

  where f is a discounting factor.

  Source: Chuang-Stein (1994) Controlled Clin Trials.

Discounting at Patient Level

- The concept is intuitive.
- Reducing (overall) safety experience into one score requires input and agreement on the algorithms from many.
- The choice of the converting factor could be a challenge.
- At a minimum, we could look at (efficacy, safety) jointly instead of separately.

Multinomial Outcome

- Using pre-specified rule, summarize patient (efficacy,safety) outcome into categories
  - Efficacy and no serious side effect
  - Efficacy and serious side effect
  - No efficacy and no serious side effect
  - No efficacy and serious side effect
  - Side effect leading to dropout
- Assign weights to these categories to form a ratio measure or a linear score.

Source:Chuang-Stein et al (1991) Stat in Medicine

Table 1 Cross-tabulation of Patients by 30-Day Survival and Hemorrhagic Stroke for Each Treatment Group in the GUSTO Trial

	No Hemorrhagic Stroke	Hemorrhagic Stroke	Row Total
Panel A			
Streptokinase			
30-day Death	1409	64	1473
30-day Survival	18660	40	18700
		$((\hat{p}\hat{q})_S = 40/20173 = 0.00198)$	$(\hat{p}_S = 18700/20173 = 0.927)$
Column Total	20069	104	20173
		$(\hat{q}_S = 104/20173 = 0.00516)$	
Panel B			
t-PA			
30-day Death	609	43	652
30-day Survival	9661	31	9692
		$((\hat{p}\hat{q})T = 31/10344 = 0.00300)$	$(\hat{p}_T = 9692/10344 = 0.937)$
Column Total	10270	74	10344
		$(\hat{q}_T = 74/10344 = 0.00715)$	

Number of patients in cell (proportion of patients in cell for that treatment group).

Source: O'Neill (2006) Society for Clinical Trials Meeting

Global Benefit-Risk (GBR) Measure

Six treatment response categories were defined on the bases of efficacy and AEs:

- category I, response with **no** AEs;
- category II, response with **mild** AEs;
- category III, response with **moderate** to **severe** AEs;
- category IV, no response and no AEs, or discontinuation for lack of efficacy or a reason unrelated to treatment;
- category V, no response with **mild** AEs;
- and category VI, no response with **moderate** to **severe** AEs, or discontinuation for AEs regardless of response.

Source: Entsuah & Gorman (2002) *J Psy Research,* 36:111-118.

Global Benefit-Risk (GBR) Measure

- Assume the six categories occur with prob $\{p_i\}$.
- One can form a benefit/risk measure as below where e (≥ 0) reflects the importance of efficacy.

$$r = \frac{(w_1 p_1 + w_2 p_2 + w_3 p_3)^e}{(w_4 p_4 + w_5 p_5 + w_6 p_6)}$$

- One can also form a linear score

$$s = w_1 p_1 + w_2 + p_2 + \ldots + w_6 p_6$$

Source: Pritchett & Tamura (2008), Pharm Stat, 7(3):170-178

Prescription Drug Facts: AMCID (amoditine)

What is this drug for?	To relieve heartburn
Who might consider taking it?	Men and women bothered by heartburn or acid reflux disease
Who should NOT take it?	Women who are pregnant or breastfeeding
Recommended testing	None
Other things to consider doing	Eat frequent small meals; avoid fatty foods (and others which trigger your symptoms); excessive alcohol and eating close to bedtime; don't smoke; look into other medications.

AMCID Study Findings Box

500 people with bothersome heartburn were given AMCID or a sugar pill for 2 weeks. Here's what happened:

What difference did AMCID make?	People given a sugar pill	People given AMCID (20 mg a day)
Did AMCID help? Fewer people taking AMCID had heartburn (17% fewer)	81% 810 in 1000	64% 640 in 1000
Did AMCID have side effects?		
Life threatening side effects No difference between AMCID and a sugar pill	None observed	
Symptom side effects		
No difference in headache	About 5% in both groups 50 in 1000	
No difference in diarrhea	About 2% in both groups 20 in 1000	
No difference in dizziness	About 1% in both groups 10 in 1000	

How long has the drug been in use?

Amcid was approved by FDA in 1991 - Studies show that most serious side effects or recalls of new drugs happen during their first 5 years of approval.

Woloshin and Schwartz
Drug Facts Box

FDA Risk Communication
Advisory Committee Meeting

Feb 26-27, 2009

PhRMA Benefit Risk Action Team

- Formed in 2006 with key objectives:
  - Formulate a framework for the ideal benefit-risk approach, including a methodology for integrating both qualitative and quantitative elements in an evolutionary way.
  - Provide greater structure and transparency for sponsor company - FDA alignment throughout approval process.
- BRAT partnered with RTI Health Solutions epidemiologists to complete the work in 2009.

PhRMA Benefit-Risk Framework

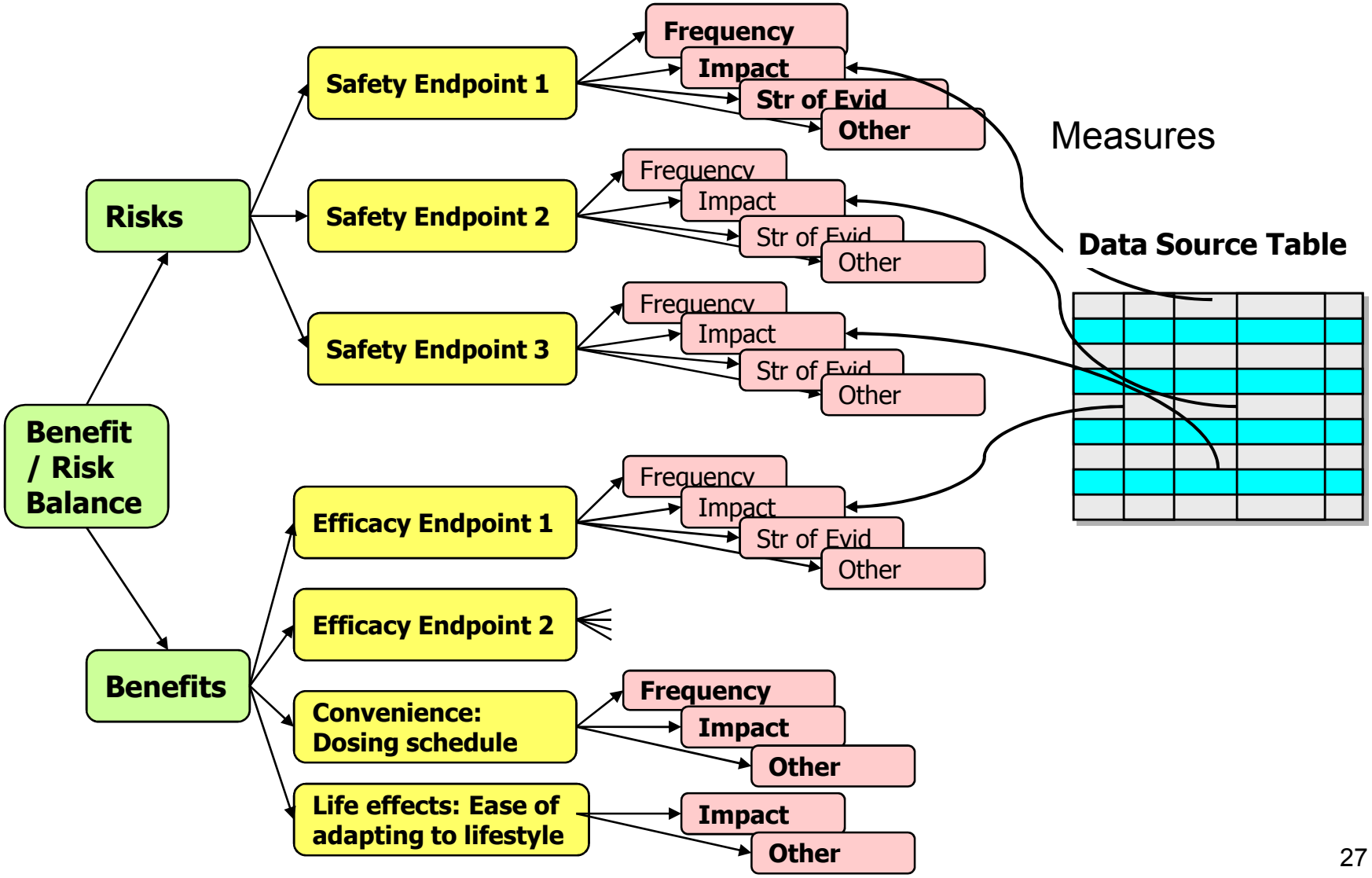
- The Vision
  - The framework can be considered a set of processes and tools to guide decision-makers in structuring, summarizing and interpreting the information.
  - Framework should be adaptable for different contexts depending on the type of information collected and structured, but the fundamental of the framework remains the same.
- The Work
  - There will be 3 rounds of development and testing (statins, tumor necrosis factor – alpha antagonists, and triptans), using mock products in different therapeutic categories.

Envisioned Steps of Framework

- Establish the Decision Frame.
- Identify the Benefit and Risk Outcomes (selections and definitions)
- Choose the Metrics - the specific measurements to quantify benefit and risk outcomes
- Identify and Organize the Data Source
- Adapt the Value Tree, Data Source and Summary Tables
- Calculate the Metrics – apply weights where applicable for quantitative assessment
- Interprete the Assessment – visualization method or approach

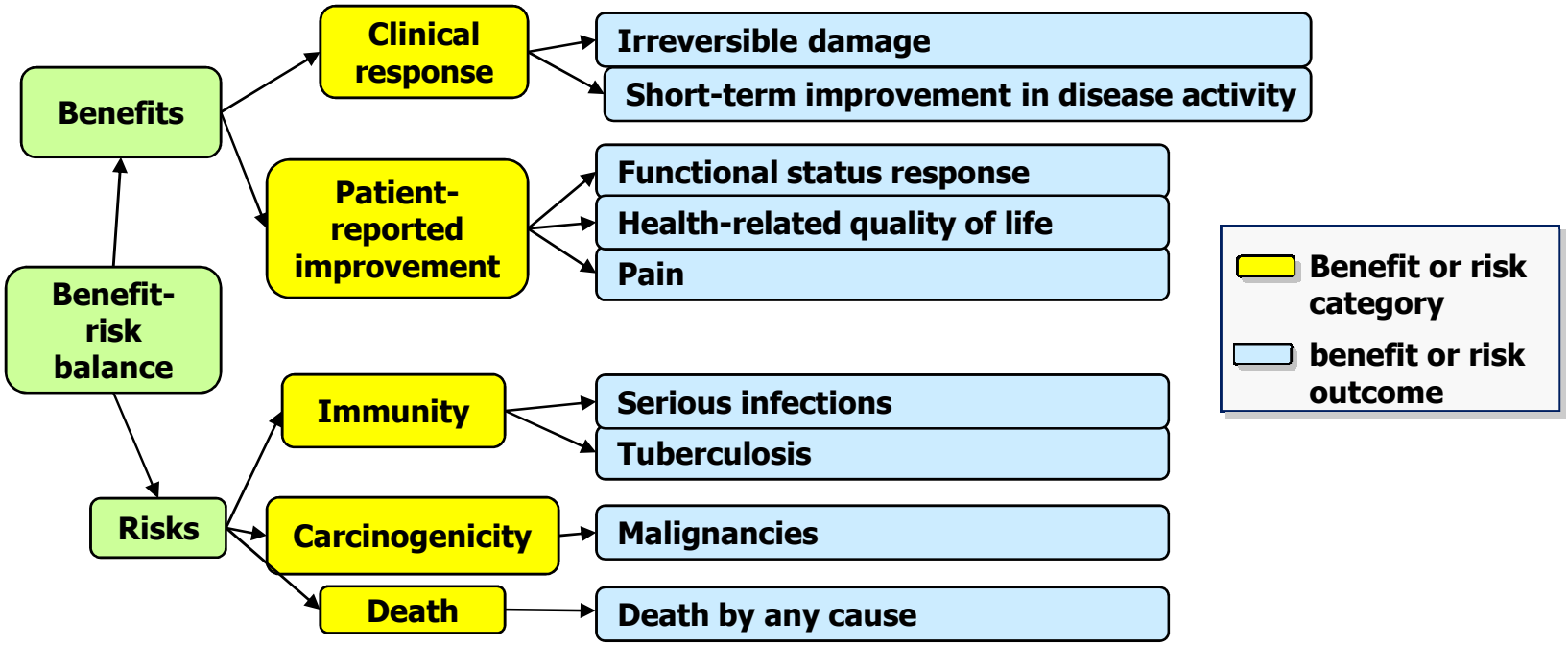
Source: PhRMA BRAT Framework Project Round 2 (slides 26-31), 8 March 2010

Framework Process



TNF- α Blockers for Rheumatoid Arthritis

- Repeated tuning led to the following framework.
- Solid malignancies, lymphoproliferative cancers, and nonmelanoma skin cancers combined into one category "malignancies"

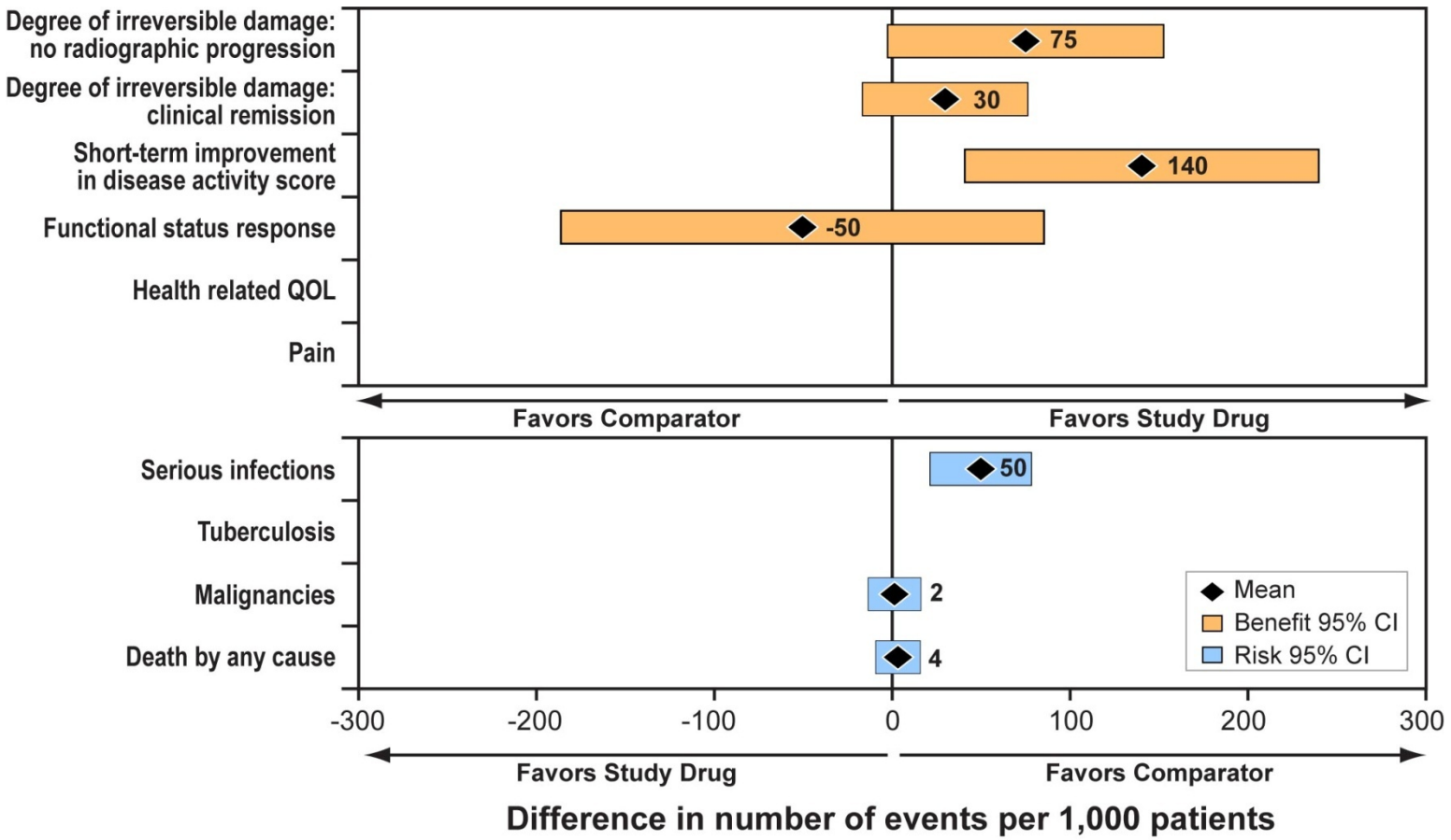


Key Benefit-Risk Summary Table

		Outcome	Outcome Measure	Study Drug (%)	Active Comparator (%)
Benefit	Clinical response	Degree of irreversible damage	No radiographic progression (change in Sharp score < 0.5)	39.2	31.8
			Clinical remission (DAS < 1.6 or DAS28 < 2.6)	14.0	10.9
		Short-term improvement in disease activity score	ACR-20 response at 14 weeks	51.9	37.9
	Patient-reported improvement	Functional status response	HAQ-DI clinically meaningful improvement (≥ 0.22 units)	58.0	63.0
Risks	Immunity	Serious infections	Proportion of patients	10.5	5.5
		Tuberculosis	Proportion of patients	0.0	0.0
	Malignancies	Malignancies	Proportion of patients	1.4	1.2
	Death	All cause death	Proportion of patients	0.7	0.2

Difference in # of Events per 1,000 Patients

- Graphical displays help with interpretation of data
- There are 2 different axes for Benefit and Risk data on this version (Benefit= positive outcome, Risk = negative outcome)



Drill Down For ACR-20 Response

		Outcome	Outcome Measure	Study Drug (%)	Active Comparator (%)	Relative Risk (95% CI)
Benefit	Clinical response	Degree of irreversible damage	No radiographic progression (change in Sharp score < 0.5)	39.2	31.8	1.24 (1.04-1.47)
			Clinical remission (DAS < 1.6 or DAS28 < 2.6)	14.0	10.9	1.28 (0.92-1.77)
		Short-term improvement in disease activity score	ACR-20 response at 14 weeks	51.9	37.9	1.37 (1.16-1.62)
	Patient-reported improvement	Functional status response	HAQ-DI clinically meaningful improvement (≥ 0.22 units)	58.0	63.0	0.92 (0.80-1.06)
		Health-related quality of life	No binary data	---	---	No data
		Pain	No binary data	---	---	No data
Risks	Immunity	Serious infections	Proportion of patients	10.5	5.5	1.92 (1.38-2.66)
		Tuberculosis	Proportion of patients	0.0	0.0	No events
	Malignancies	Malignancies	Proportion of patients	1.4	1.2	1.21 (0.50-2.90)
	Death	Death by any cause	Proportion of patients	0.7	0.2	2.69 (0.28-25.72)

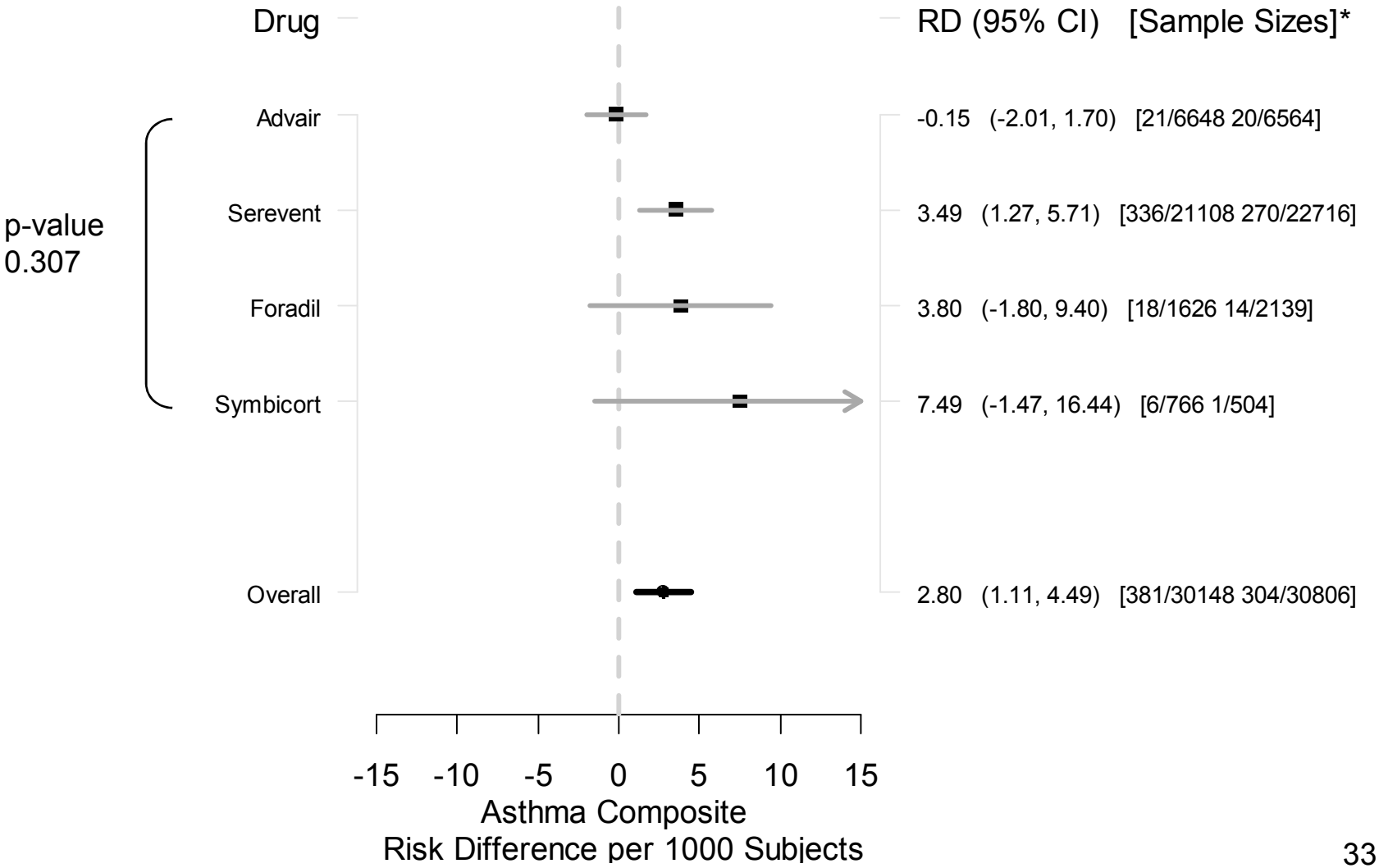
Odds Ratio Supporting Studies for ACR-20

Study ID	Study drug # events	Study drug N	Active Comparator # events	Active Comparator N	Relative Risk	95% CI	Timepoint
4	47	133	37	133	1.27	(0.89 - 1.82)	24 weeks
7	76	103	14	50	2.64	(1.67 - 4.17)	24 weeks
5	82	159	79	160	1.04	(0.84 - 1.30)	24 weeks

Who Makes Benefit:Risk Decisions?

- A joint meeting on Dec 11 2008 in the US to weigh the public health implications of real and serious but relatively infrequent occurrences of severe asthma exacerbations and asthma-related death against the symptomatic benefits of bronchodilation and asthma control of long-acting beta-agonists (LABAs).
  - Pediatric Advisory Committee
  - Pulmonary-Allergy Drugs Advisory Committee
  - Drug Safety and Risk Management Advisory Committee
- Safety data came from 110 randomized trials of 4 LABAs.
- Risk assessment was based on a composite endpoint of asthma-related death, intubation, or hospitalization.

Risk Difference



*RD = Risk Difference Per 1000 Subjects
[Treat. Events/Treat. n Plac. Events/Placebo n]

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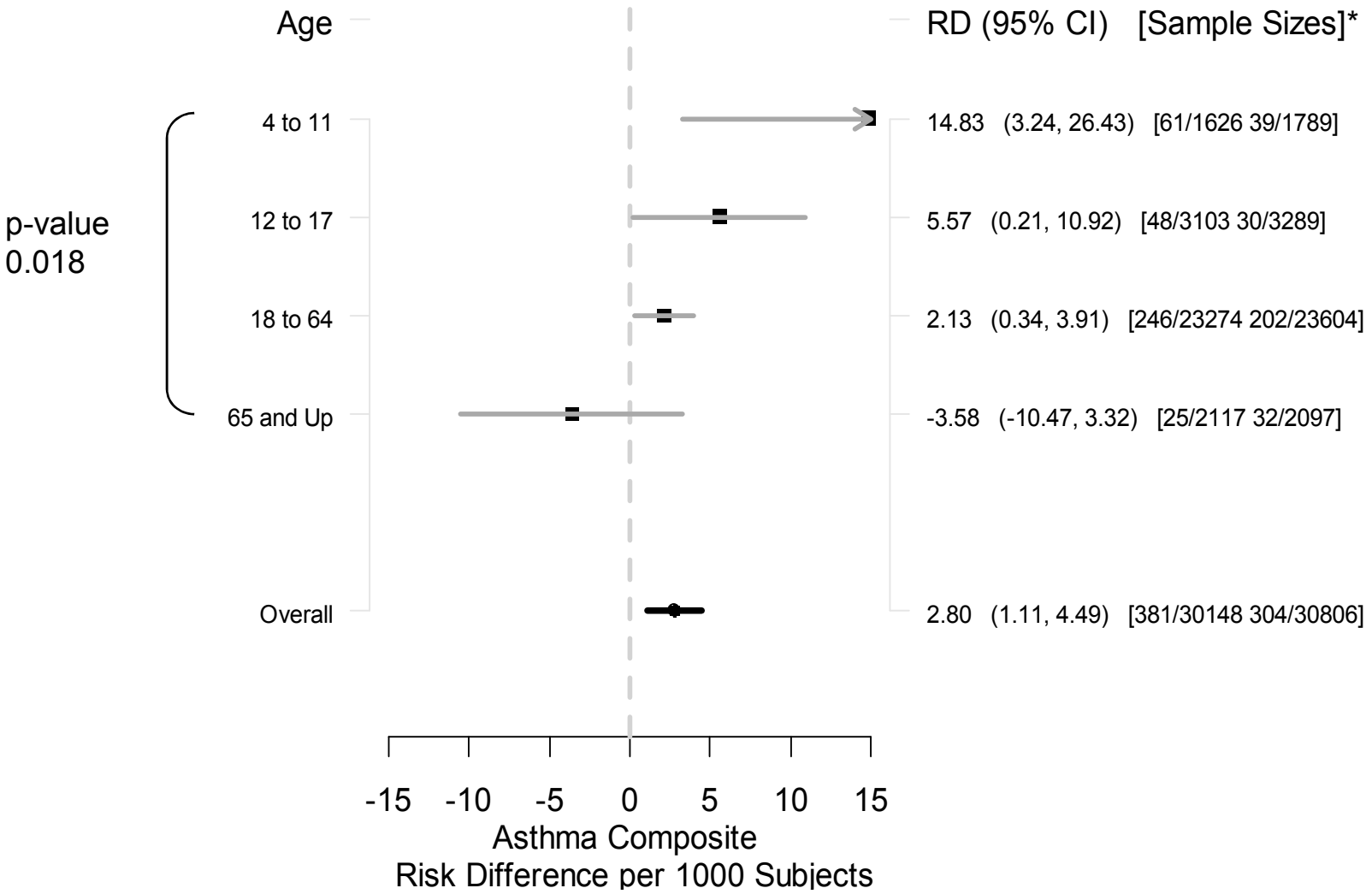
Risk Difference by Age Groups



*RD = Risk Difference Per 1000 Subjects
[Treat. Events/Treat. n Plac. Events/Placebo n]

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Different Views

- FDA Office of Surveillance and Epidemiology recommended removing the asthma indication from single-entity LABAs (i.e. not in combination with corticosteroids) for all patients.
- FDA Division of Pulmonary and Allergy Products concerned that removing the asthma indication would limit clinicians' options for treating asthma that cannot be controlled by inhaled corticosteroids alone.
- Who should decide on the values of benefits and risks? Regulators, committee members, health care professionals, patients or payors? Are there other major stakeholders?

Source: Kramer, NEJM, April 16 2009.

Summary

- FDA is frequently asking questions like “Do the risks outweigh the benefits”. This is a shift from asking separate questions on safety and effectiveness only.
- The first step in benefit-risk assessment is to agree on the relevant data elements for a specific case.
- It is difficult to settle on a single set of values. It may be necessary to show how the overall conclusion depends on the specific choice of values.
- Eventually, a judgment needs to be made at the societal and/or individual level.