



SOCIETY OF DECISION
PROFESSIONALS
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Presenting:

All is Never Really Said and Done: Actively Navigating Benefit and Risk

Marilyn Metcalf, PhD

DAAG Conference 2013

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All is Never Really Said and Done: Actively Navigating Benefit and Risk

Marilyn Metcalf, PhD

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DAAG 2013

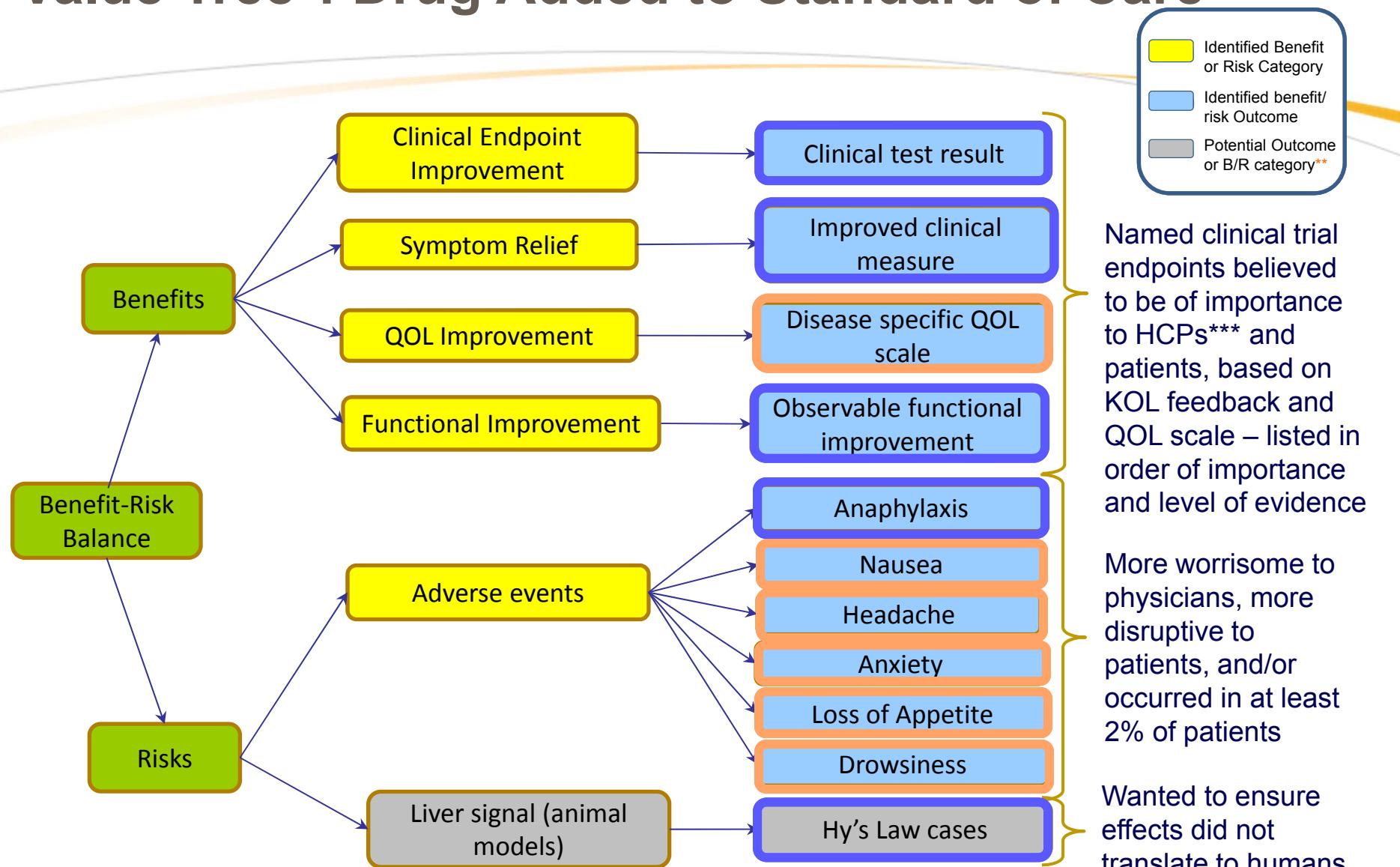
What do we mean by Benefit and Risk?

- **Benefit:** what we want a treatment to do for patients and what is important about the outcomes
 - Clinically relevant outcomes or biomarkers / surrogates that are considered favorable effects and rationale for choosing them
 - Intensity, duration, and uncertainty of effects
- **Risk:** the potential consequence to the patient and how to manage the events when they occur
 - Clinically relevant outcomes or biomarkers / surrogates that are considered unfavorable effects
 - Severity, duration, predictability, “monitorability,” and reversibility of effects
- **Benefit-Risk Balance:** how the favorable effects compare to the unfavorable effects

The Case

- Real questions and solutions based on cumulative experience
- Unnamed drug and condition
- Disguised benefits and risks
- Condition has bothersome symptoms
- Medication is needed chronically
- Case study:
 - How benefits and risks were chosen
 - How drug was compared to alternative treatment
 - How team presented its case
 - Plans for this year

Value Tree*: Drug Added to Standard of Care

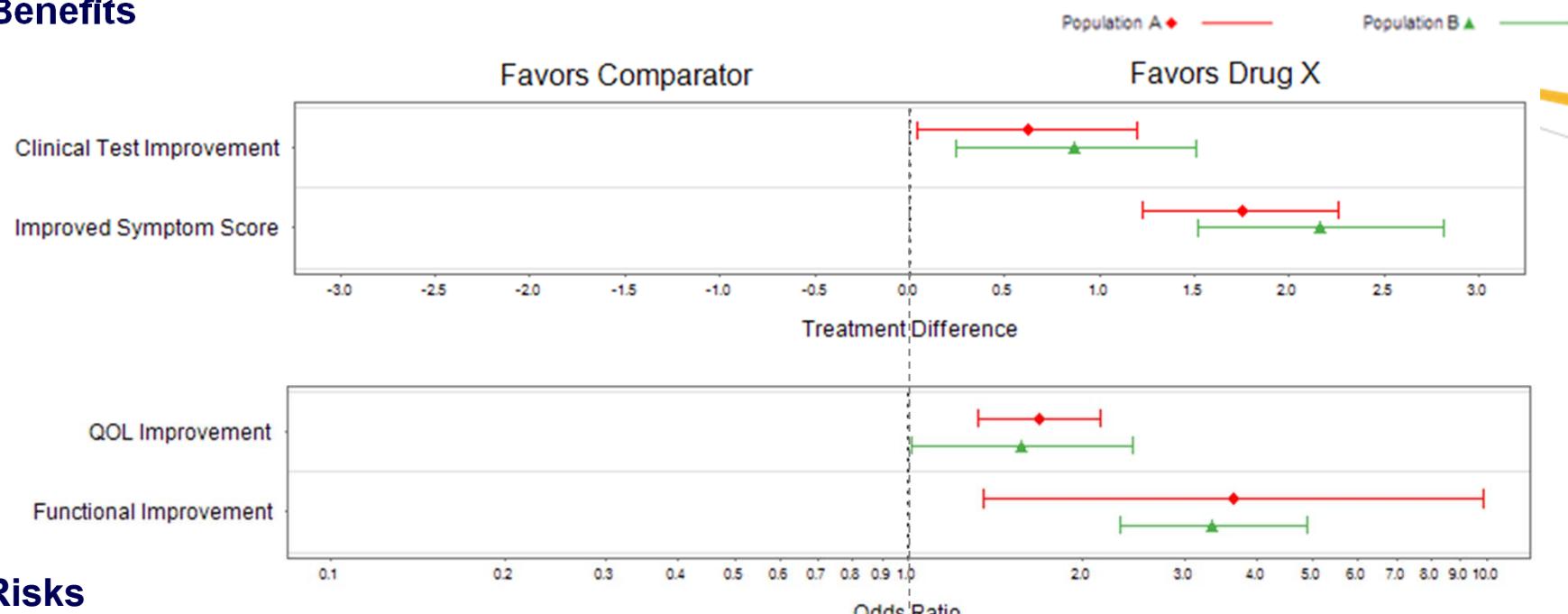


*from PhRMA BRAT Framework; EMA has successfully field tested a similar "effects tree"

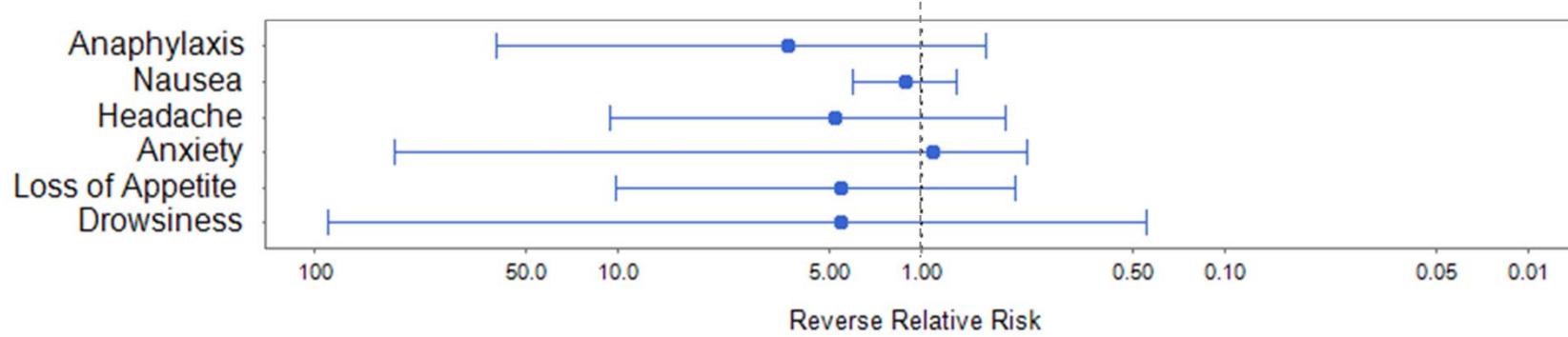
** relationship to treatment not proven; ***HCPs=healthcare providers

Graph for Internal BR/Safety Review

Benefits



Risks



Comparator (Standard of Care) vs. Drug (point estimate and 95% CI)

Benefits are from 1 year and 2 year Populations: Phase 3 studies (n=400);

Risks are from Primary Safety Population: Phase 3 studies and Phase 2 study (n=600)

No Hy's Law Cases

5

If it's on the tree, it should be in the graph, or you should know why not.

Making the Comparison

- Teams began the process based on their next milestone, so in this case, C2MD (POC) had been achieved and measures of benefit and risk were aligned to efficacy and safety clinical trials that had been chosen for pivotal studies
- Add-on therapy naturally looks for incremental benefit and risk v. standard of care, so comparator was SOC
- Benefits were measured on different scales, therefore shown with different axes; “no difference” measures were aligned, and there was some attempt to keep scales to comparable size among sections of the graph
- Risk measures were reversed to move in the right direction v. the benefit measures
- No summary measure of incremental net benefit or other overall “score” was used. The graph acted as a backdrop for discussion with safety board.
- Two populations (same condition) had been studied; rather than combine them, their measures were color coded to show benefit in each group [Note: this approach also works well when background rates are needed to provide context for benefit or risk.]
- Differences among sources of data were noted

Of Note

- The case addressed comparison among options, but there is also a question of whether there is a positive BR balance within the drug itself (i.e., v. not treating)
- This is often a question when a first treatment is introduced; the assumption may be that any treatment is better than none, but this may not be the case
- The same methods and discussions would apply, regarding the nature and amount of benefit v. how much risk would be attained, and how well the risk could be managed / mitigated / minimized
- Assessments occur throughout a treatment's lifecycle

Pharmacovigilance

- Benefit was pretty straightforward, so questions focused on helping patients navigate risk, ***now and in the future***
- Looked for ways to identify patients most at risk for anaphylaxis
- Ensured team would include proper warnings to HCPs and patients around signs, symptoms; considered potential first dosing in presence of HCP if necessary
- Noted need for further understanding of severity of headache
- Team was given action to explore and address drowsiness issues regarding possible need for additional warnings around driving, use of heavy machinery, etc., or whether bedtime dosing would be an alternative solution; would there be a “hangover” effect?

Patients' BR trade-offs may be based on their goals for treatment, e.g.,

Disease Prevention

- safe
- minimally invasive
- durable effect

Acute life-saving

- effective
- immediate
- manageable AEs

Chronic treatment

- durable
- minimal AEs
- convenience for desired activity level

End of Life

- minimal AEs
- based on desire for hospital, hospice, or home care

Chronic disease delay

- durable
- manageable AEs
- convenience for desired activity level

Curative

- targeted
- durable
- manageable AEs

Key Benefit-Risk Questions to Answer

Priority Depends on Treatment Goals	Benefits	Risks
Intensity	How good are they?	How severe are they?
Time	How soon do they happen?	How soon do they happen?
	How long do they last?	How long do they last?
Probability	Do they only happen for some people?	Can they be avoided? If no, can they be managed?

Provide information needed for BR trade-offs, e.g.:

Chronic for degenerative

- durable
- manageable AEs
- convenience for desired activity level
- How can I preserve my ability to walk for as long as possible?
- What can you tell me about my personal risk for a fatal or life-threatening AE? What would be the signs to look for?

Disease Prevention

- safe
- minimally invasive
- durable effect
- What can you tell me about the risks of this disease, which seem minimal, compared to the risks of giving my healthy child this vaccine? Why should I contribute to “herd immunity”?
- Can’t you make it less painful?

Priority Depends on Treatment Goals	Benefits	Risks
Intensity	How good are they?	How severe are they 2
Time	How soon do they happen?	How soon do they happen?
	How long do they last? 1	How long do they last?
Probability	Do they only happen for some people?	Can they be avoided? If no, can they be managed? 3

Priority Depends on Treatment Goals	Benefits	Risks
Intensity	How good are they?	How severe are they 1
Time	How soon do they happen?	How soon do they happen?
	How long do they last? 3	How long do they last? 2
Probability	Do they only happen for some people?	Can they be avoided? If no, can they be managed?

Benefit-Risk is continuing to grow

2011

"Just try to put benefit and risk together in one graph."

2012

- Most teams with milestone reviews presented BR
- Guidance slides for framing, graphing, writing a brief
- Safety Board and Safety Leader feedback

1Q 2013

- More diverse products
- More proactive work from teams

Response to Feedback:

- BR Framework
- Synergies with other work
- BR Basics Training (N=280+ names for invitations); Advanced Training later in 2013



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This talk:

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Was slightly modified from the original talk to remove several images on the slides. If you would like a copy of the original slide set, please send your request to: marilyn.a.metcalf@gsk.com

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