

Patient-focused Benefit-Risk Assessment



March 4, 2016


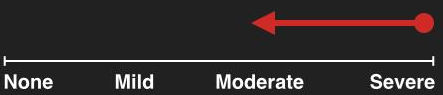
NIH HCS Collaboratory and PCORnet Grand Rounds



Bennett Levitan, MD-PhD

Department of Epidemiology

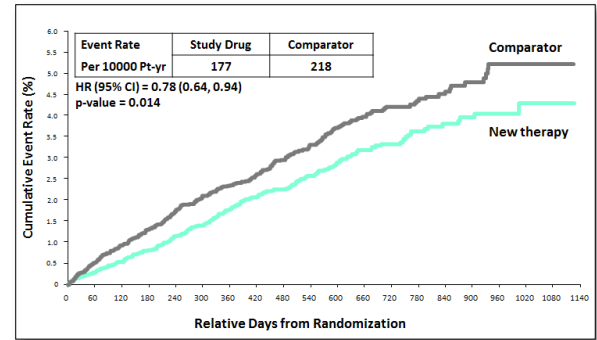
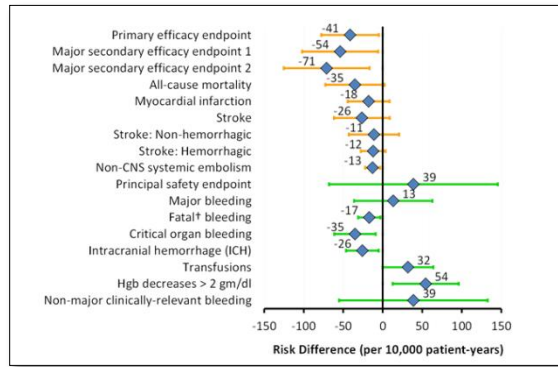
Janssen Research & Development, LLC

Outcome	Drug A	Drug B
Relief of pain	 <p>A horizontal scale with four points: None, Mild, Moderate, and Severe. A red arrow starts at the Severe point and points left towards the Mild point.</p>	 <p>A horizontal scale with four points: None, Mild, Moderate, and Severe. A red arrow starts at the Severe point and points left towards the Moderate point.</p>
Ability to perform work/school and social activities	No limitations	Cannot work, difficulty with chores and shopping
Annual chance of a heart attack	1 in 10,000	No chance
Which medicine would you choose if these were the only medicines available?	<input data-bbox="929 829 993 891" type="checkbox"/>	<input data-bbox="1412 829 1476 891" type="checkbox"/>

Outcome	Drug C	Drug B
Relief of pain	 <p>A horizontal scale with four points: None, Mild, Moderate, and Severe. A red arrow starts at the Severe point and points left towards the Mild point.</p>	 <p>A horizontal scale with four points: None, Mild, Moderate, and Severe. A red arrow starts at the Severe point and points left towards the Moderate point.</p>
Ability to perform work/school and social activities	No limitations	Cannot work, difficulty with chores and shopping
Annual chance of a heart attack	1 in 1,000	No chance
Which medicine would you choose if these were the only medicines available?	<input data-bbox="927 828 994 892" type="checkbox"/>	<input data-bbox="1410 828 1477 892" type="checkbox"/>

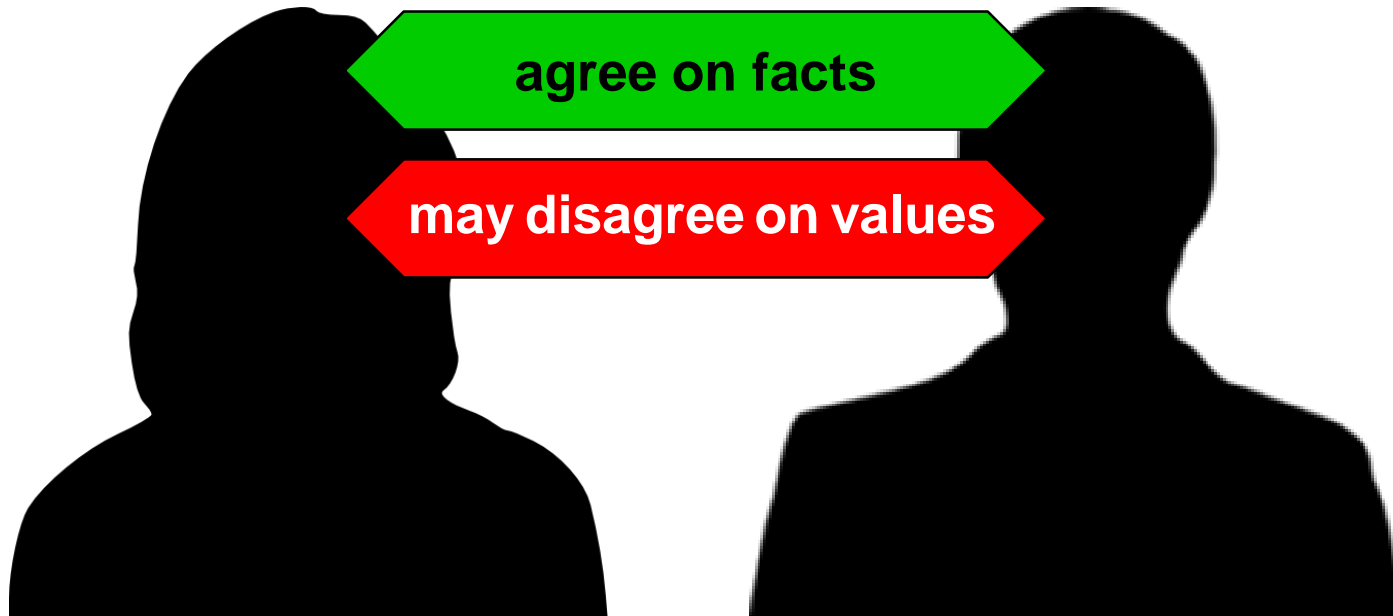
Outcome	Drug D	Drug B
Relief of pain	 <p>None Mild Moderate Severe</p>	 <p>None Mild Moderate Severe</p>
Ability to perform work/school and social activities	No limitations	Cannot work, difficulty with chores and shopping
Annual chance of a heart attack	1 in 100	No chance
Which medicine would you choose if these were the only medicines available?	<input data-bbox="927 828 994 892" type="checkbox"/>	<input data-bbox="1410 828 1477 892" type="checkbox"/>

Endpoint	Study Drug/ 10,000 pt-yrs	Comparator Rate/ 10,000 pt-yrs	HR (95% CI)	Risk Difference / 10,000 pt-yrs
Primary efficacy (Stroke + embolism)	177	218	0.78 (0.65, 0.94)	-41 (-78, -5)
Secondary efficacy 1 (stroke, embolism + vascular death)	318	371	0.85 (0.73, 0.98)	-54 (-102, -6)
Secondary efficacy 2 (stroke, embolism + vascular death + MI)	396	467	0.84 (0.73, 0.95)	-71 (-125, -17)



physician

patient



What Did Migraine Patients Say?

Stated choice conjoint preference survey of 200 adult migraine patients

- **Relieving all functional limitations was twice as important as relieving all migraine pain**

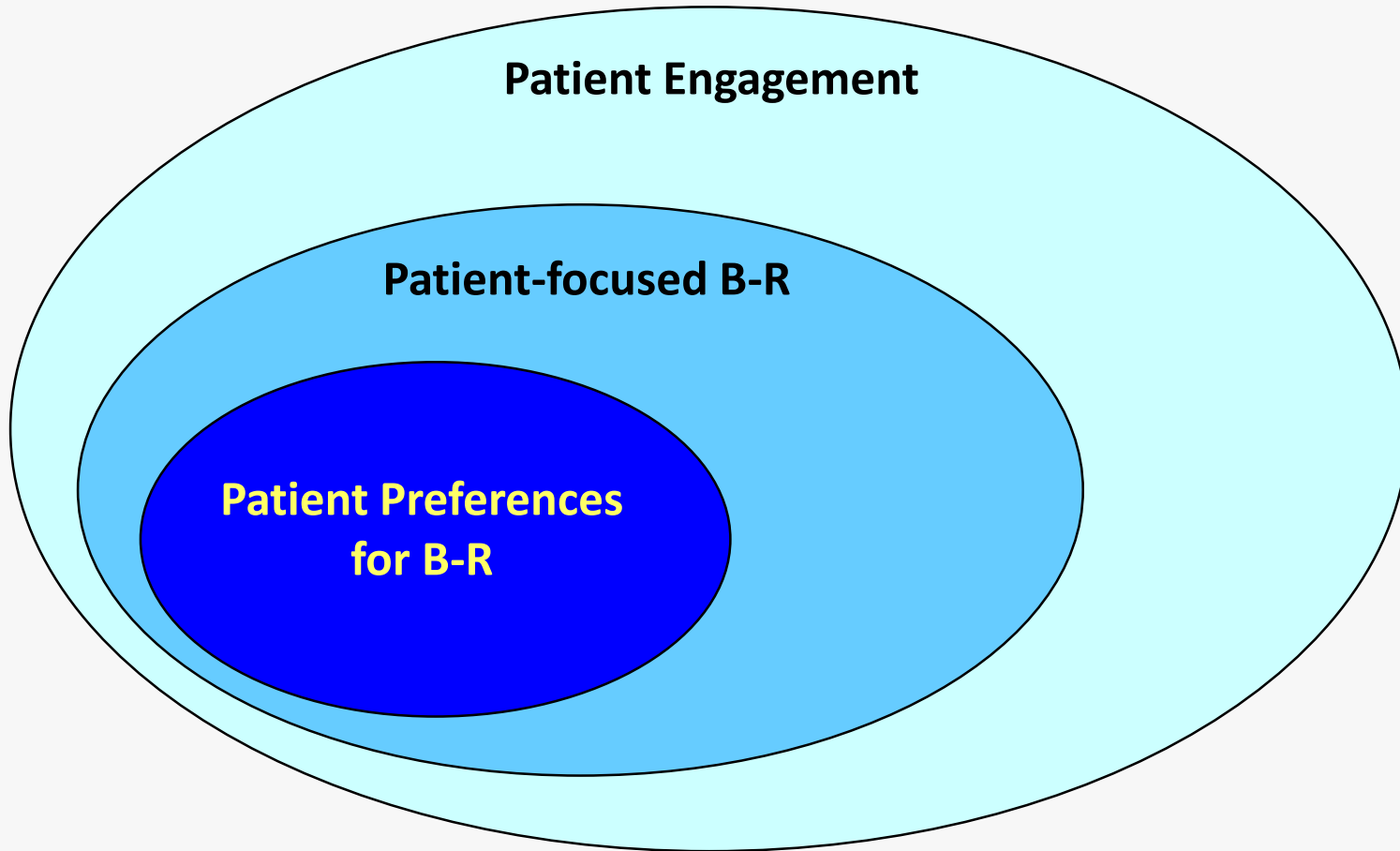
Maximum Acceptable Risk = maximum level of treatment-related 1-year heart attack risk patients would accept for a given improvement in migraine symptoms

- **Patients would accept up to a 2/1000 (95% CI 1.6 – 2.4) annual heart attack risk in exchange for restoring their ability to function during migraines**

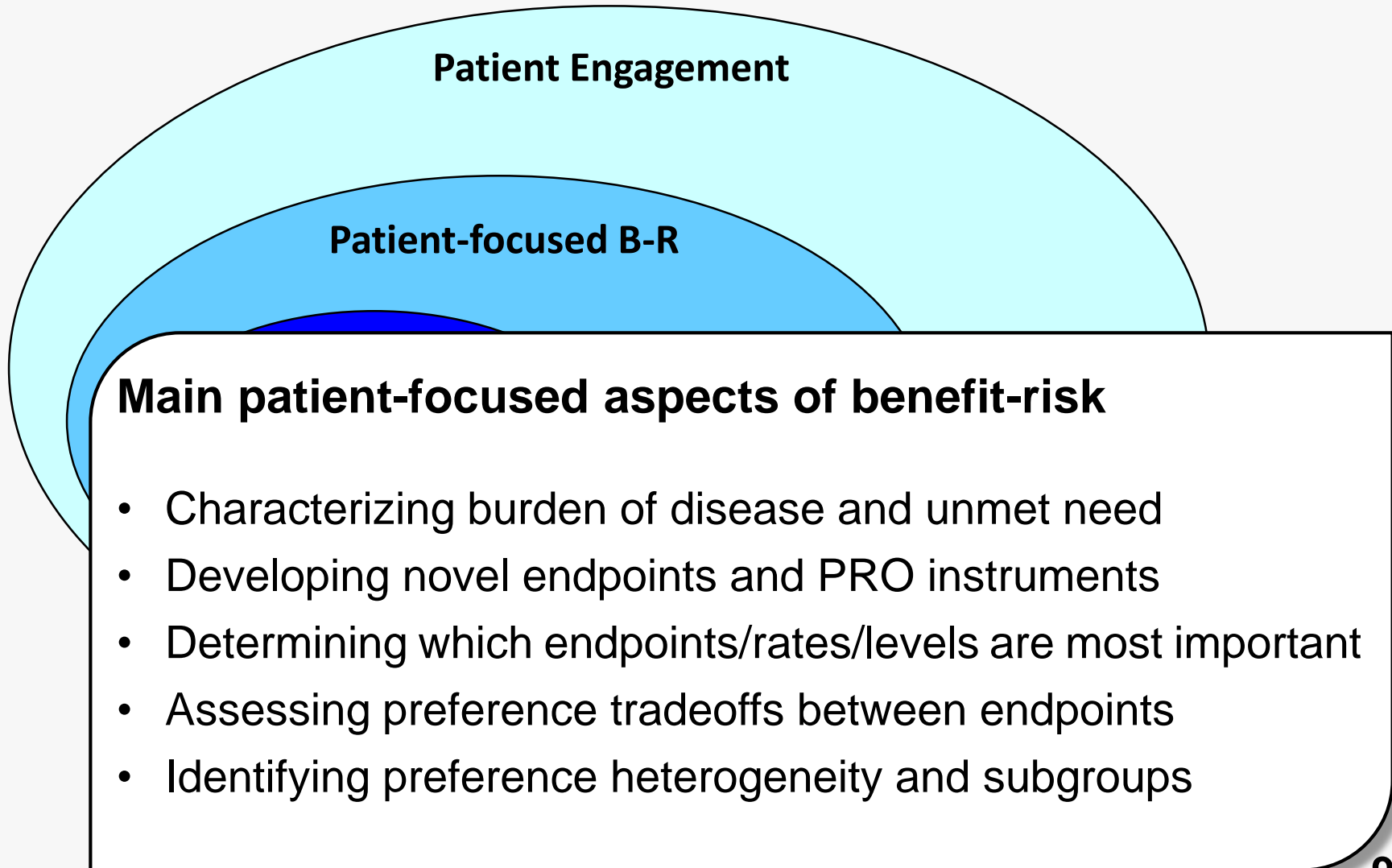
Benefit-risk Assessment

- **Evaluation of medical products considering both benefits and harms**
 - ▶ Not simply the union of efficacy and safety data
- **Key component of FDA, EMA and other health authority regulatory decisions**
 - ▶ Unstructured in the past, becoming more formal
- **A growing field combining regulatory, clinical, decision, behavioral economics and risk communication sciences**

Patient Engagement, Patient-focused B-R and Patient Preferences



Patient Engagement, Patient-focused B-R and Patient Preferences



Growing Regulatory and Patient Momentum for Patient-focused Drug Development / B-R

Regulatory (selected)



FDA CDER B-R Framework

Decision Factor	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	Summary of evidence:	Conclusions (implications for decision):
Current Treatment Options	Summary of evidence:	Conclusions (implications for decision):
Benefit	Summary of evidence:	Conclusions (implications for decision):
Risk	Summary of evidence:	Conclusions (implications for decision):
Risk Management	Summary of evidence:	Conclusions (implications for decision):
Benefit-Risk Summary and Assessment		

FDA's "Voice of the Patient" Report Series

Patient views become part of B-R Framework

FDA B-R Framework

The Voice of the Patient

A series of reports from the U.S. Food and Drug Administration's (FDA's) Patient-Focused Drug Development Initiative

Chronic Fatigue Syndrome and

Public Meeting: April
Report Date: September

The Voice of the Patient

A series of reports from the U.S. Food and Drug Administration's (FDA's) Patient-Focused Drug Development Initiative

Lung Cancer

Public Meeting: June 28, 2013
Report Date: December 2013

Center for Drug Evaluation and Research
U.S. Food and Drug Administration

Center for Drug Evaluation and Research (CDER) and
Center for Biologics Evaluation and Research (CBER)
U.S. Food and Drug Administration (FDA)

Sample ME-CFS Benefit-Risk Assessment Framework

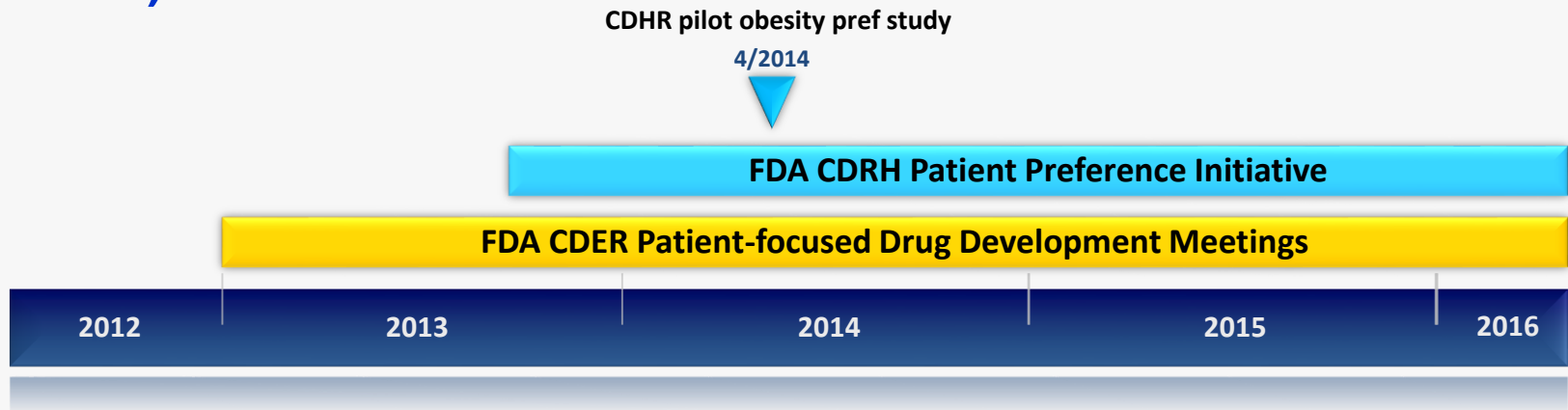
Decision Factor	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	<ul style="list-style-type: none"> CFS and ME is a chronic multi-system disorder characterized by profound fatigue lasting for six or more months that is not improved by bed rest and that may be worsened by physical or mental activity. The disease may occur with a sudden or gradual onset. Symptoms often include impaired cognitive functioning, severe fatigue or exhaustion, unrefreshing sleep, chronic pain, tender lymph nodes, sore throat, orthostatic intolerance, and sensory sensitivities. The nature and severity of symptoms vary from person to person. Many patients experience post-exertional crashes, which may occur without upon even minimal physical or exertion and is associated with a exacerbation of these symptoms. 	<p>CFS and ME is a serious disease. It is a highly variable disease and may manifest in different ways from person to person. It severely affects day-to-day functioning, and some patients struggle with the simplest tasks of daily life. CFS and ME has had devastating effects on many patients' lives.</p>

Sample Benefit-Risk Framework for Lung Cancer: Analysis of Condition and Current Treatment Options

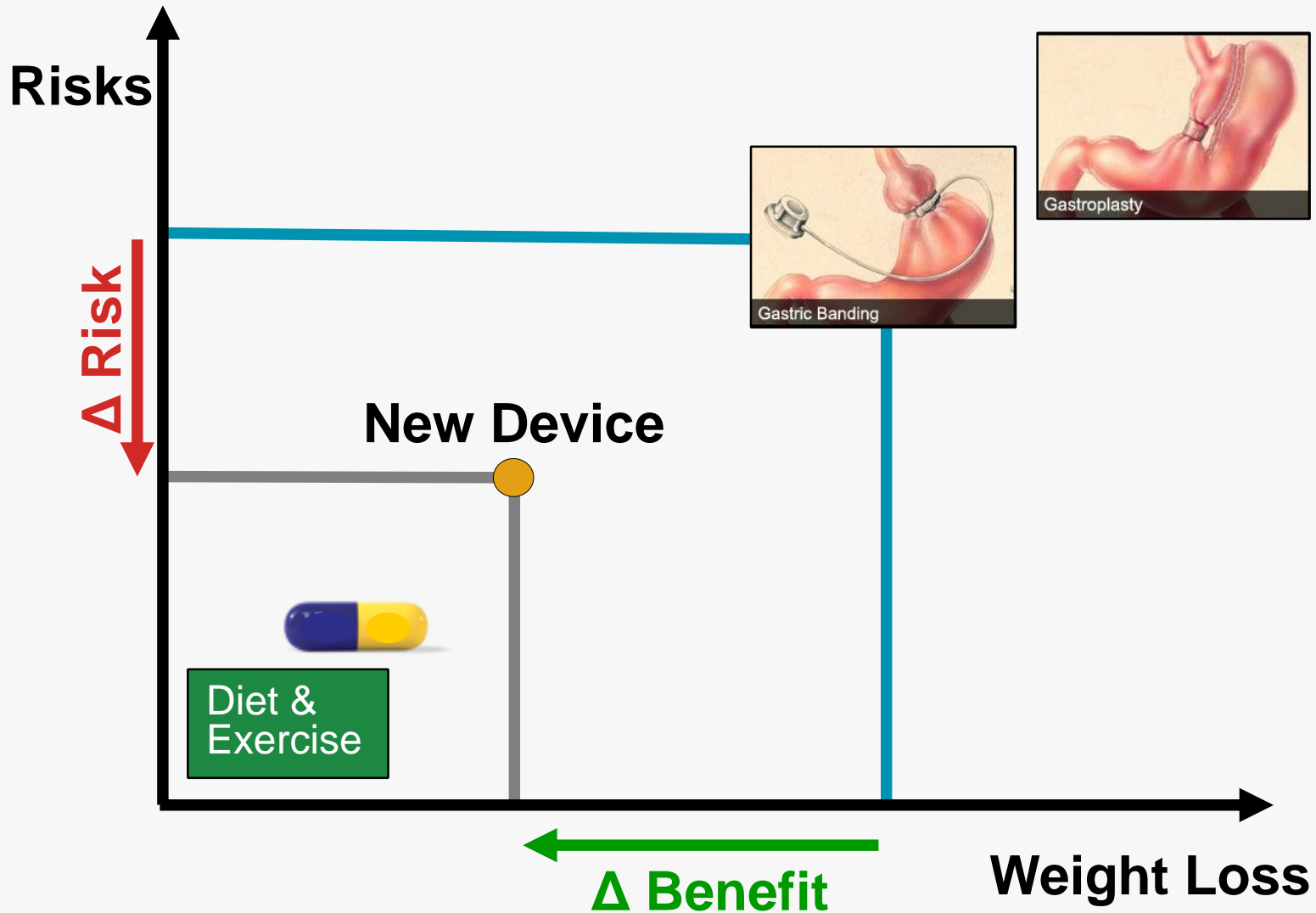
Decision Factor	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	<ul style="list-style-type: none"> There are more than 200,000 new cases and ~160,000 deaths from lung cancer every year. Prognosis depends on the type and stage of lung cancer. The average 5-year survival rate for NSCLC is ~15%. Over 50% of patients are diagnosed at an advanced stage, once the cancer has spread (metastasized) to the brain, bones, and other areas. Patients in early stages of lung cancer may not experience any symptoms. When symptoms do appear, they can include shortness of breath or difficulty breathing, coughing, coughing up blood, pain, weight loss, and fatigue. Lung cancer and its treatment can have a significant impact on patients' ability to manage work and family life and their overall quality of life. Many patients live with uncertainty, fear, anxiety, and depression. <p>See the <i>Voice of the Patient</i> report for a more detailed description of patients' perspectives on lung cancer symptoms and impacts.</p>	<p>Lung cancer is a serious and life-threatening disease. It remains the leading cause of cancer deaths in the United States. It is a rapidly fatal disease, and prognosis is dismal. While symptoms vary depending of the type and stage of lung cancer, the disease and its treatment can have a debilitating effect on patients' lives.</p>
Current Treatment Options	<ul style="list-style-type: none"> The standard of care depends on the type and stage of the cancer. In early stages, surgery in combination with radiation therapy and/or chemotherapy can potentially be curative. In later stages, these treatments may be used to shrink or slow tumor progression or prolong life. FDA-approved chemotherapy treatments include cisplatin, paclitaxel, gemcitabine, docetaxel, pemetrexed, and others. Molecularly-targeted therapies are aimed at treating patients with specific genetic changes. FDA-approved targeted therapies include crizotinib, erlotinib, and afatinib. Patients can develop resistance to chemotherapy and targeted therapies drugs after extended use, making some treatments less effective over time. Side effects and risks vary depending on the type of treatment and can have a significant impact on patients' quality of life. Side effects of chemotherapy may include fatigue, nausea, nerve damage, cognitive impairment, hair loss, and increased risk of infection or bleeding. Side effects of targeted therapies may include rash, diarrhea, fatigue, high blood pressure, increased risk of bleeding, visual changes, lung injury, and liver injury. Palliative or supportive care therapies include supplemental oxygen, pain medications, steroids, and non drug therapies such as breathing exercises and relaxation techniques. <p>See the <i>Voice of the Patient</i> report for a more detailed description of patients' perspectives on lung cancer treatments and treatment decision making.</p>	<p>There is a continuing need for additional treatment options for lung cancer patients. While some effective treatments exist, they can only be potentially curative if the disease is diagnosed in early stages. Most treatments are toxic and their side effects can have a significant impact on patients' daily lives. Emerging targeted therapies are promising for subsets of lung cancer patients.</p> <p>The potential development of resistance to chemotherapy or targeted therapies further supports the need for an expanded treatment armamentarium.</p> <p>Patients' treatment decisions often require making difficult tradeoffs between increasing the chance to prolong life and preserving quality of life.</p>

Growing Regulatory and Patient Momentum for Patient-focused Drug Development / B-R

Regulatory (selected)

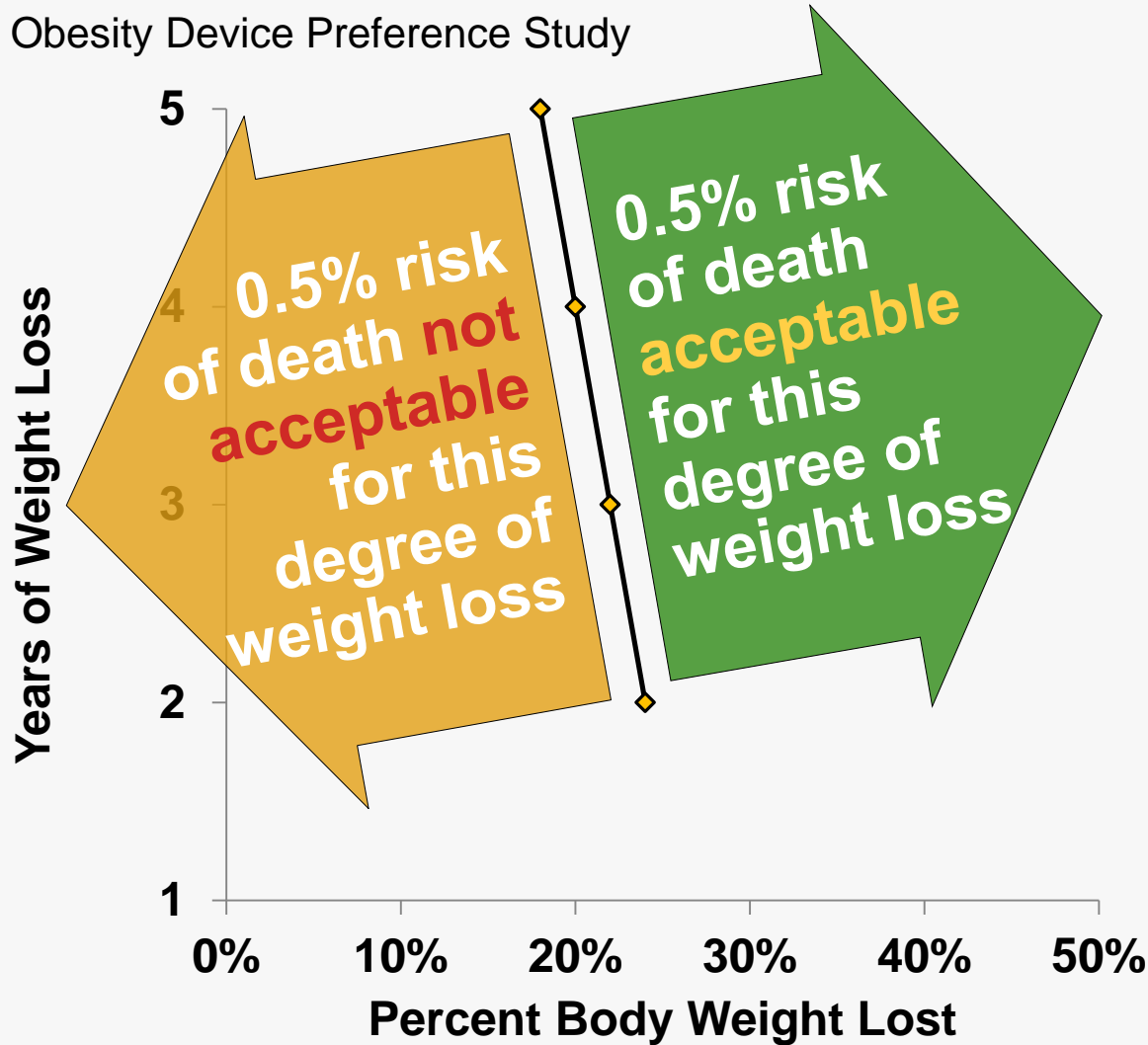


FDA CDRH Obesity Device Preference Study

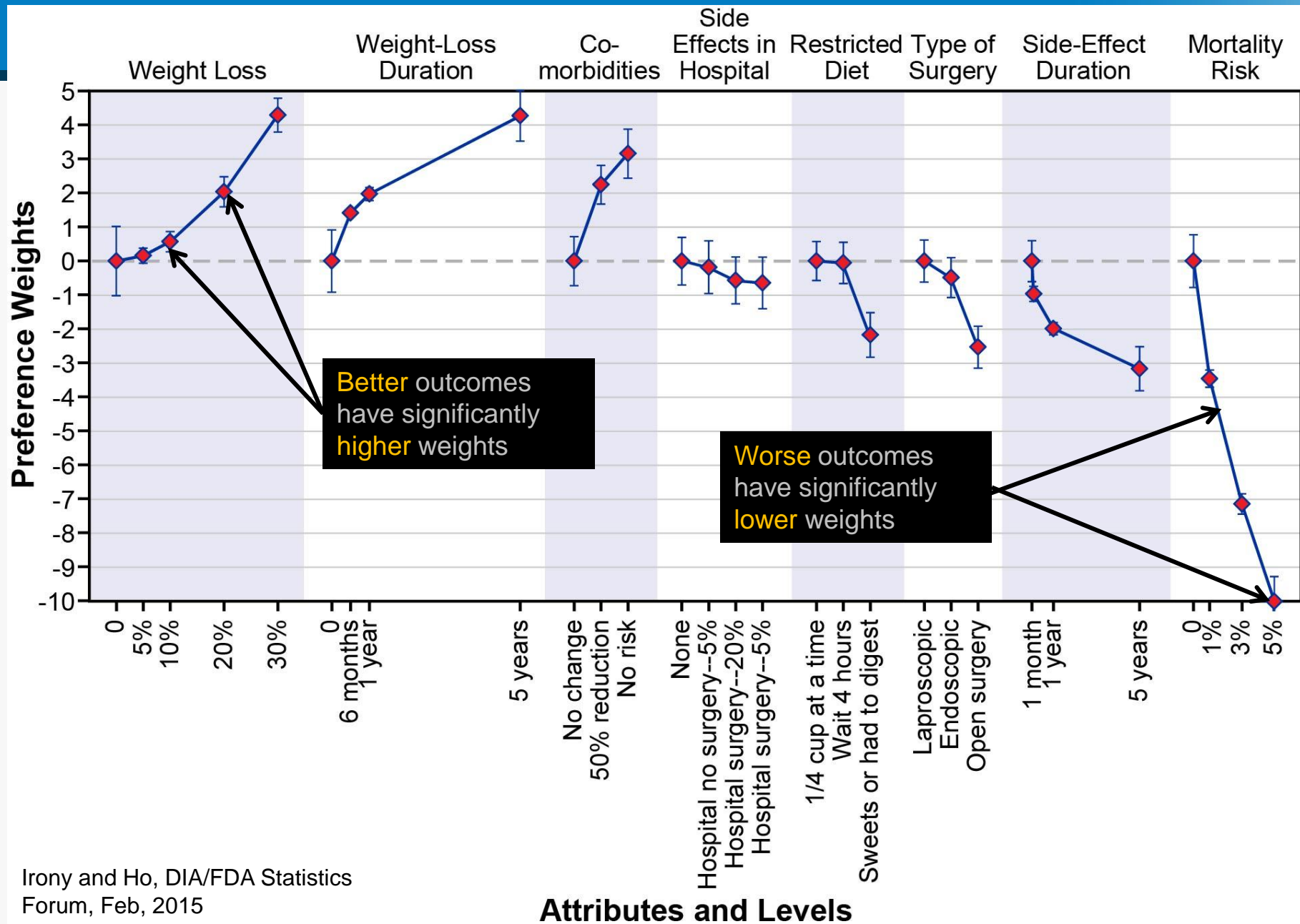


Detailed Thresholds for Maximum Acceptable Risk: Can Inform Development Strategy and Regulatory Requirements

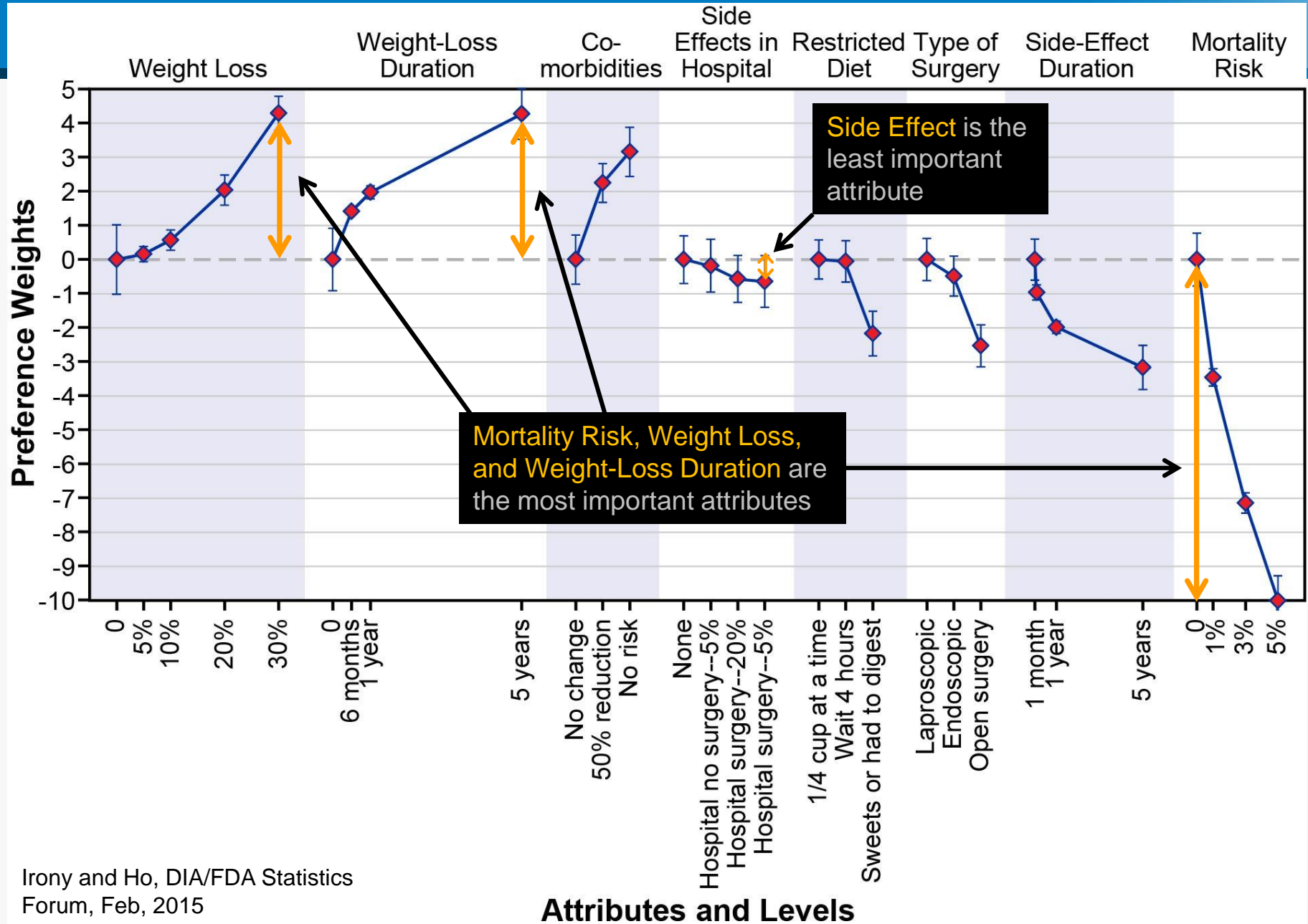
FDA CDRH/RTI Obesity Device Preference Study



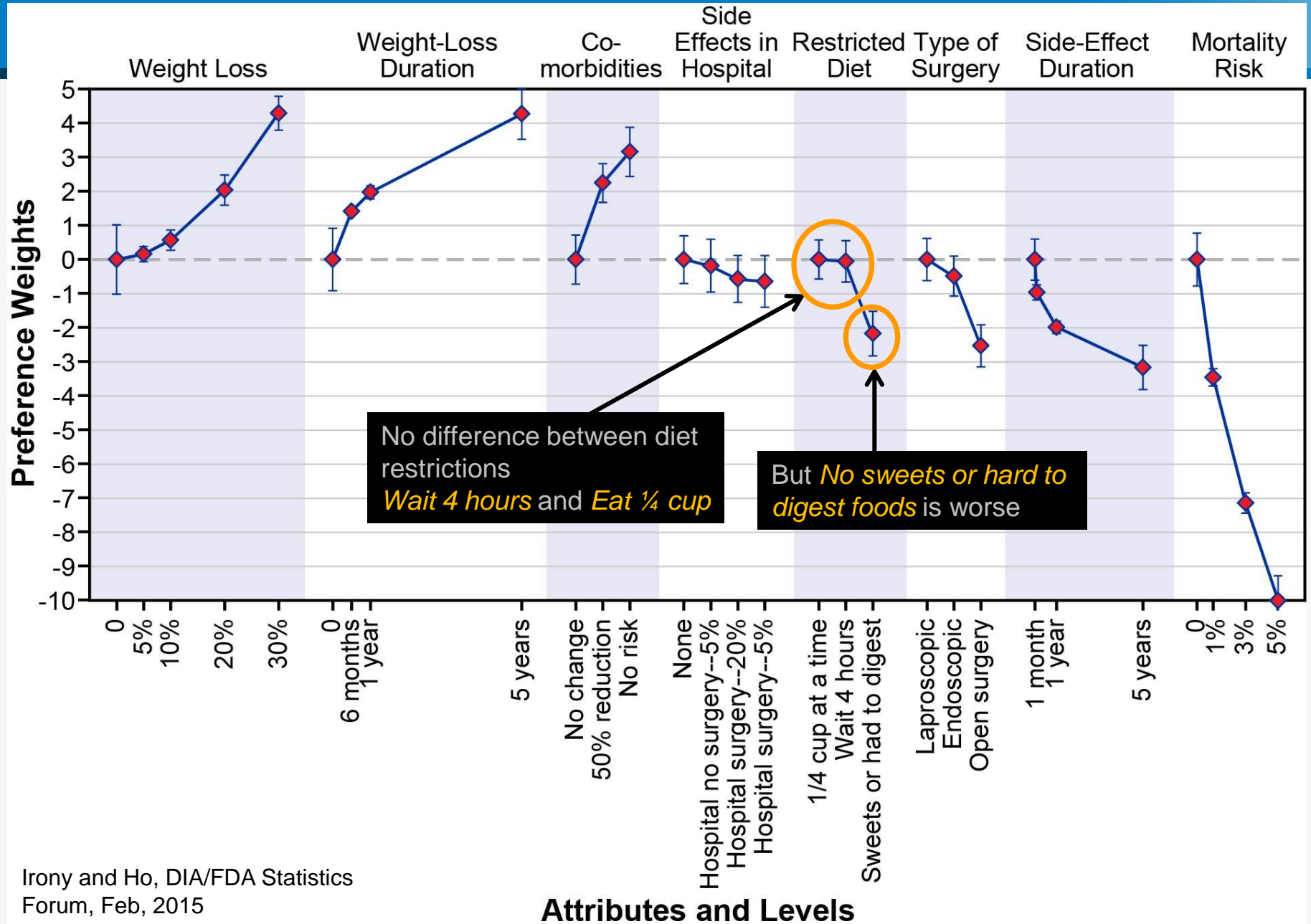
Mean Preference Weights



Mean Preference Weights



Mean Preference Weights



Can These Studies Make a Difference?

FDA Weighs Patients' Risk Tolerance in Approving Obesity Device

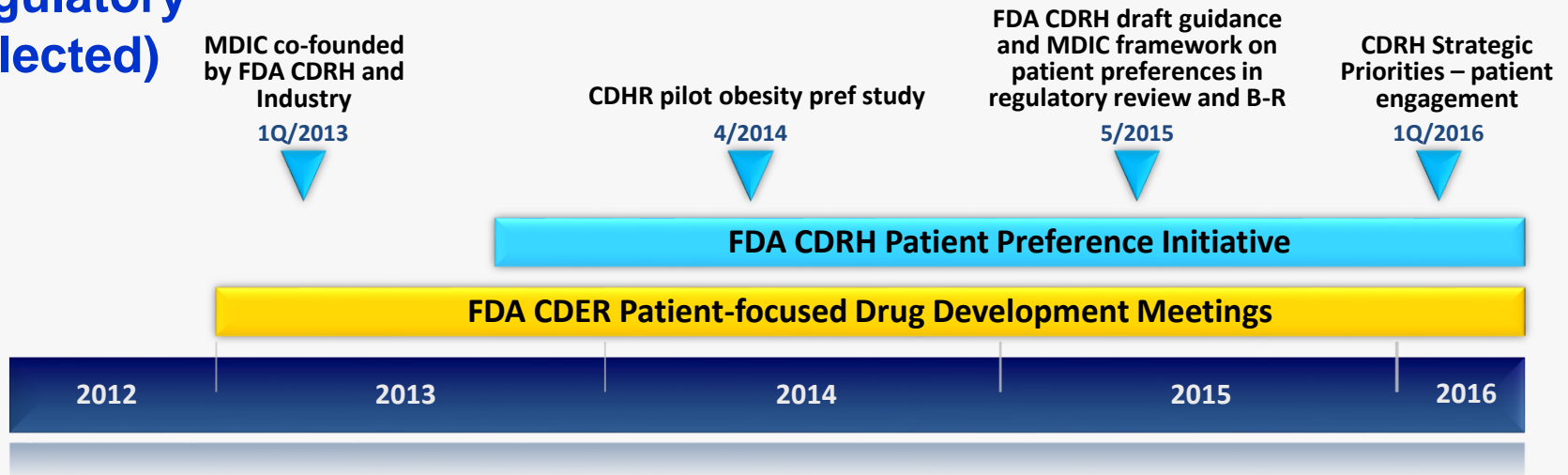
By Ferdous Al-Faruque / [Email the Author](#) / [View Full Issue](#)

The agency approved EnteroMedics' *Maestro* neuromodulator to treat obesity despite the device not meeting endpoints in its pivotal trial. The agency relied in part on a survey that found obese patients willing to take more risks in exchange for weight loss.

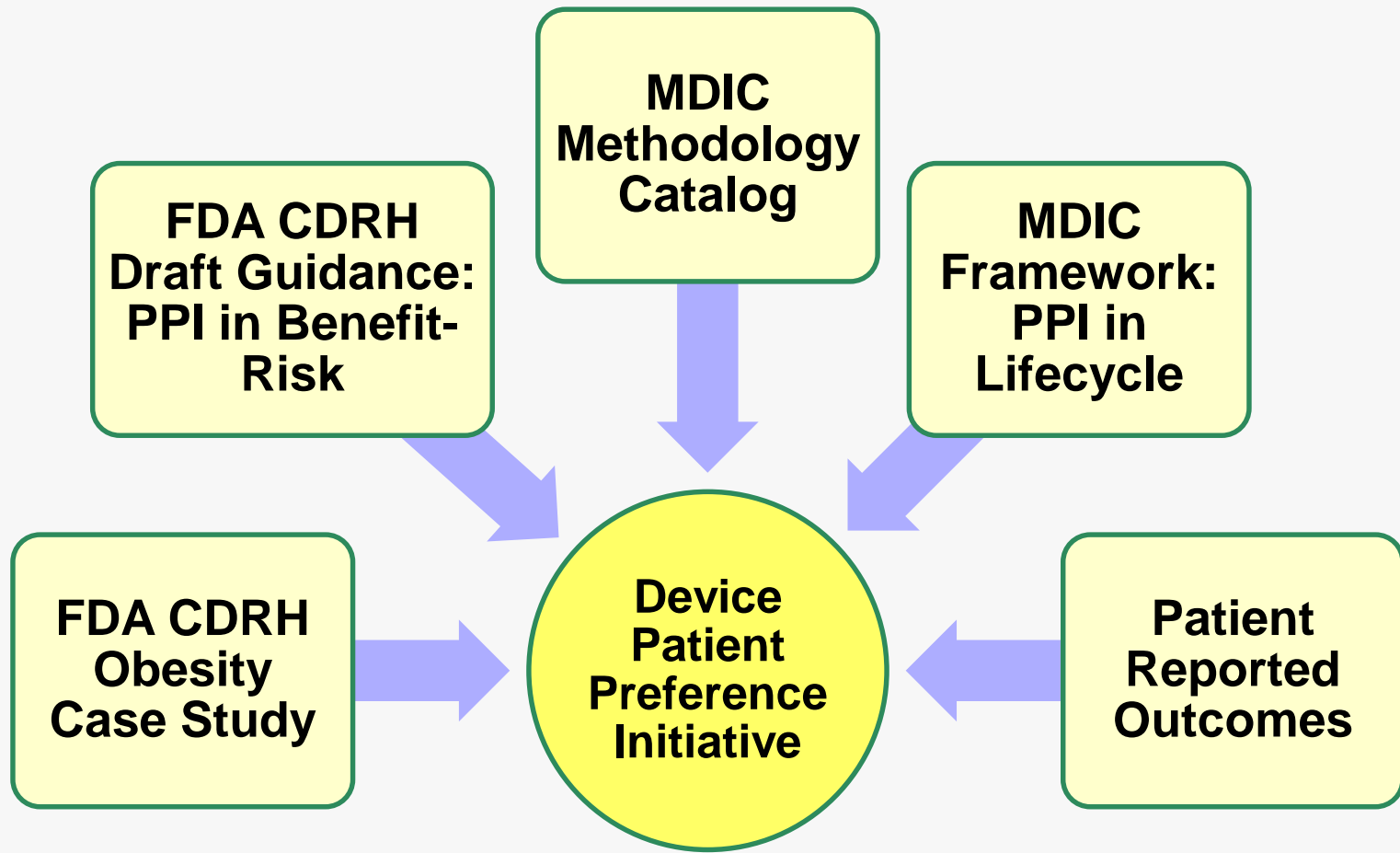
In making the decision the agency took into consideration patients' willingness to accept higher potential risk of the device which failed to meet its co-primary endpoints in a pivotal study. It is the first approval to result from CDRH's pilot program to formally incorporate patient preference into risk-benefit determinations for obesity devices, and it is the first new obesity device approved by FDA since 2007.

Growing Regulatory and Patient Momentum for Patient-focused Drug Development / B-R

Regulatory (selected)



FDA CDRH Patient Preference Initiative: Collaborative Building Blocks



PPI = Patient Preference Information



Regulatory Guidance in Benefit-Risk Assessment for Medical Devices

- FDA CDRH 2012 guidance on factors to consider for B-R assessment in devices
- Landmark regulatory policy statement on benefit-risk
- Impetus for MDIC patient-centered B-R project

Factors to Consider When Making Benefit-Risk Determinations in Medical Device Premarket Approval and *De Novo* Classifications

Document issued on March 28, 2012



Department of Health and Human Services
Food and Drug Administration

Center for Devices and Radiological Health

Center for Biologics Evaluation and
Research



Patient-Centered B-R Assessment

- **FDA CDRH guidance recognizes that patients will vary in how they value benefits and tolerate risks**
 - “FDA realizes that some patients are willing to take on a very high risk to achieve a small benefit, whereas others are more risk averse.”
 - “FDA would consider evidence relating to patients’ perspective of what constitutes a meaningful benefit when determining if the device is effective, as some set of patients may value a benefit more than others.”
- ➔ **Guidance suggests that FDA would consider patient perspective and preferences on benefits and risks**

But it did not say how...

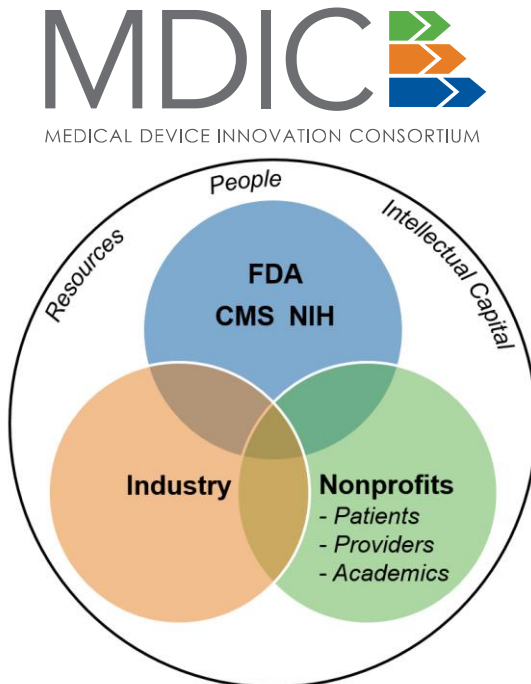


Medical Device Innovation Consortium

• 48 Members • 5 Projects

Case for Quality | Clinical Trial Innovation & Reform | Clinical Diagnostics
Computer Modeling & Simulation | Patient Centered Benefit-Risk Assessment

*A 501(c)3 - Public-Private Partnership collaborating on Regulatory Science
to make patient access to new medical device technologies faster, safer, and more cost-efficient*



Align Resources

WORKING COOPERATIVELY
with FDA to re-engineer
pre-competitive technology
innovation

Accelerate Progress

REDUCING TIME
and resources needed for new
technology development,
assessment, and review

Achieve Results

HELPING PATIENTS
gain access to new medical
technologies sooner

ALIGN | ACHIEVE | ACCELERATE

www.mdic.org



Vision for Patient-Centered Benefit-Risk Project

To establish a credible framework for assessing patient preferences regarding the probable benefits and risks of a proposed medical device and for incorporating this patient preference information into pre-market and post-market regulatory submissions and decisions



Key Components of MDIC Patient-centered Benefit-risk Framework

- Definitions and core concepts
- When is collecting patient preference information potentially valuable for B-R assessment?
- Use and value of patient preference information throughout the lifecycle
- How patient preference information may be useful in the regulatory process
- Potential value of patient preference information beyond the regulatory process
- Methods for preference assessment and factors to consider in their use

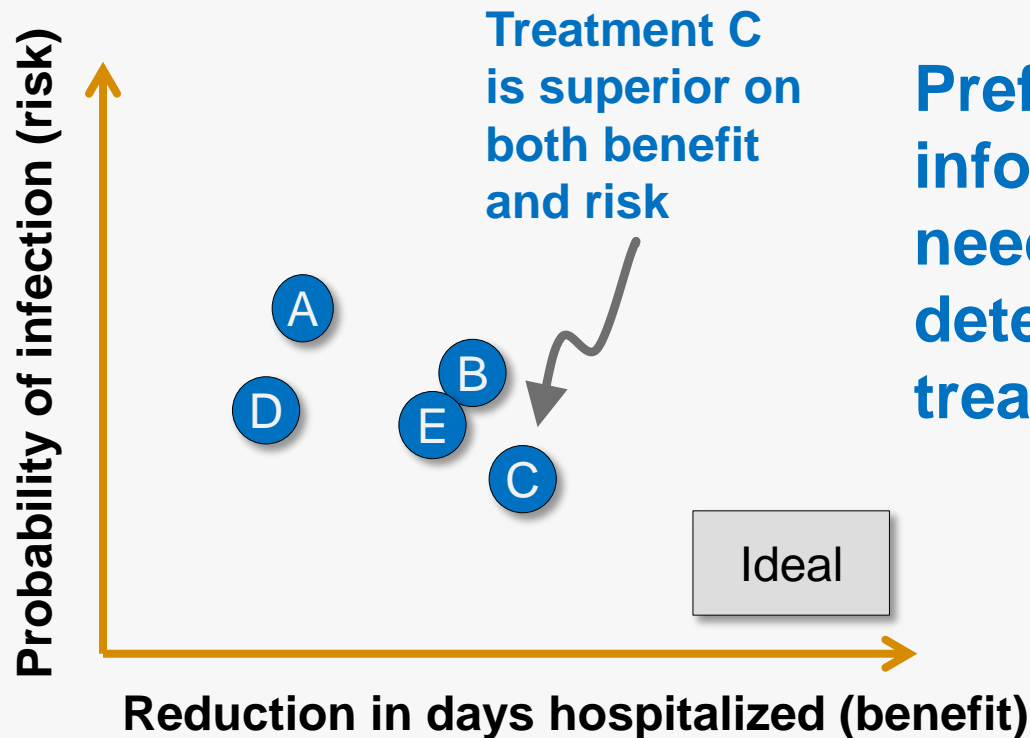


What are “Preferences”?

Qualitative or quantitative statements of the relative desirability or acceptability of attributes that differ among alternative health interventions

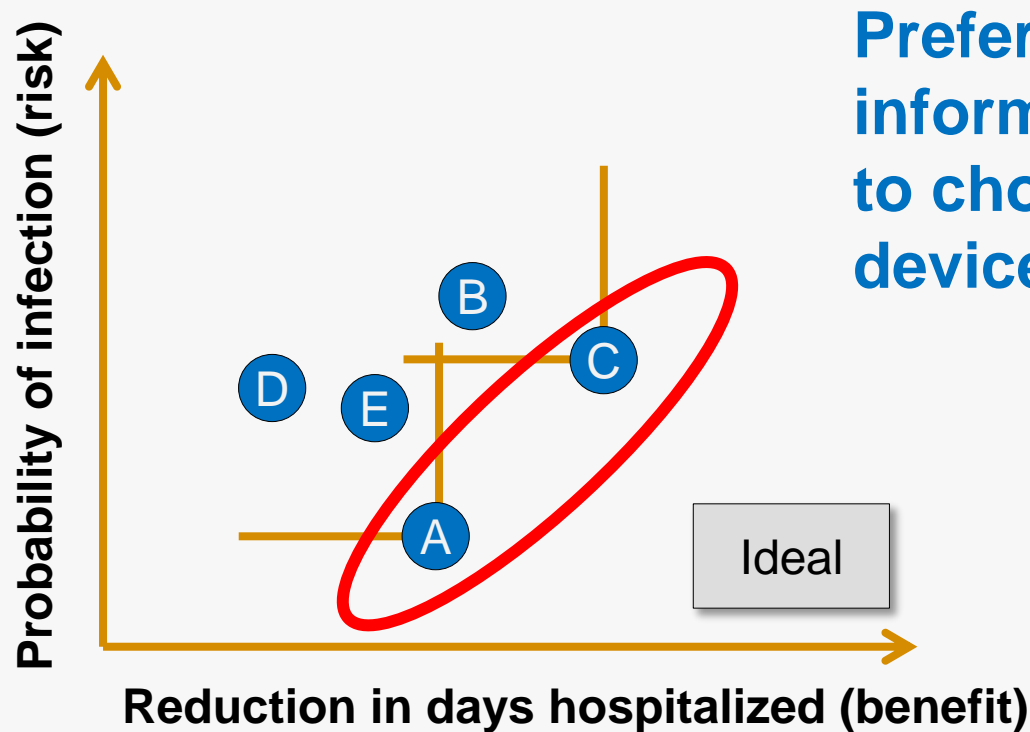
Definition applies equally well to preferences of caregivers, physicians, payers and regulators.

Which Treatment is Best?



Preference information is not needed to determine the best treatment

Now Which Treatment is Best?

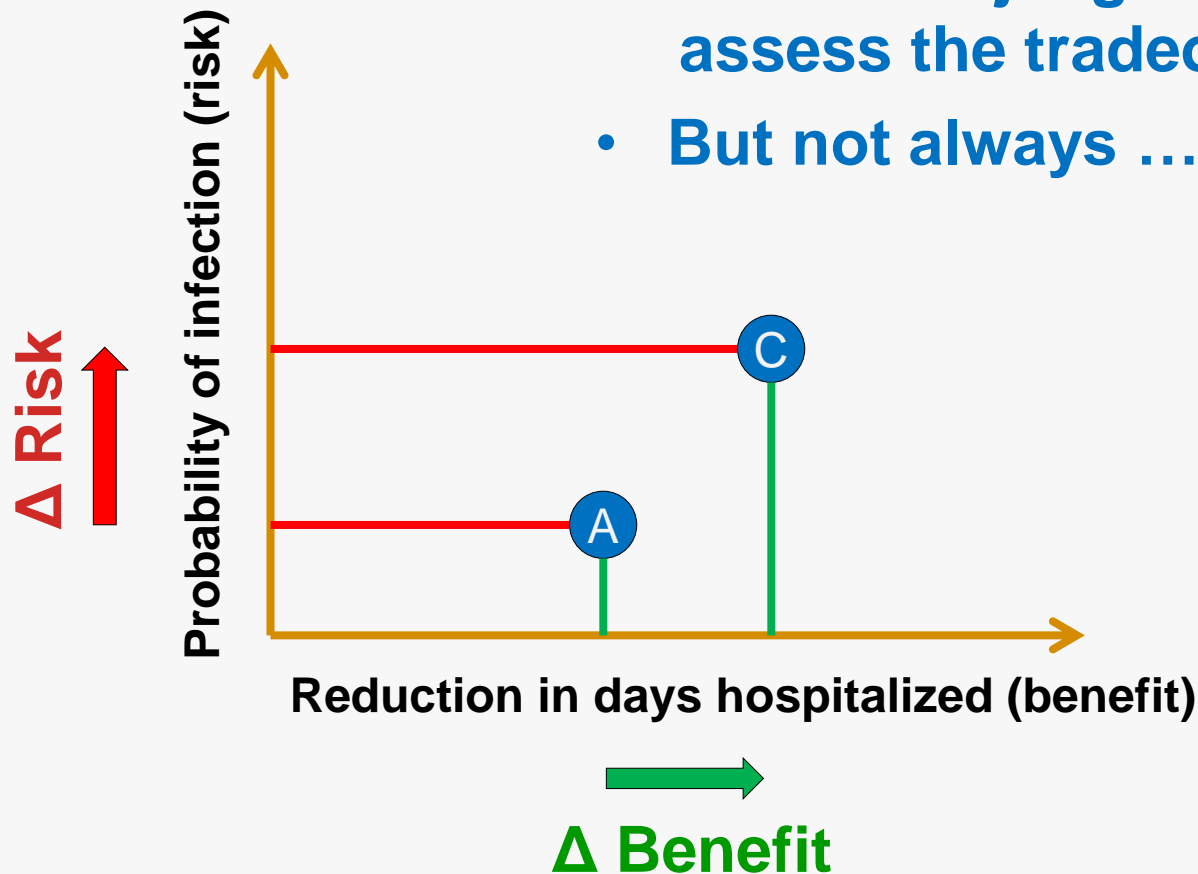


Preference information is needed to choose between devices A and Cs

This is a “Preference Sensitive Decision”

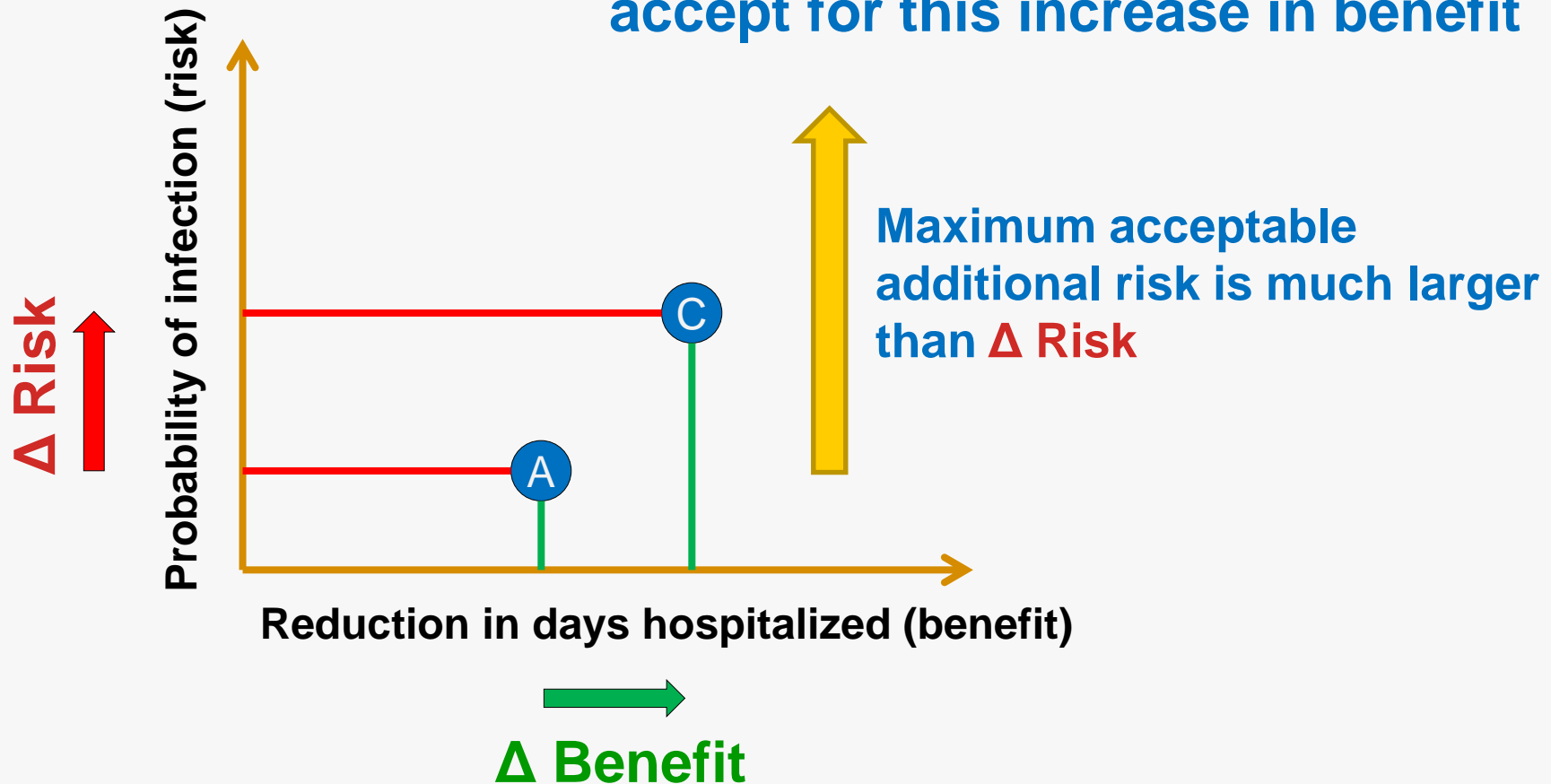
How Do Preferences Help Us Choose?

- In many cases, the decision is clear over a plausible range of preferences → clinical judgment is sufficient to assess the tradeoff.
- But not always ...



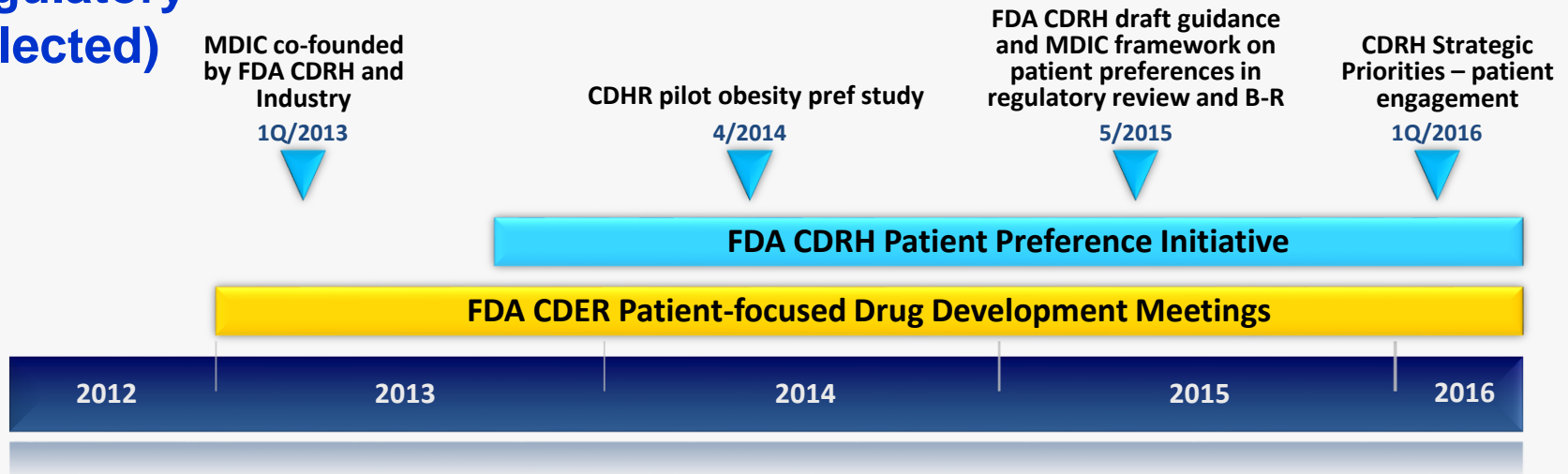
How Do Preferences Help Us Choose?

- Preference studies give the maximum additional risk that patients would accept for this increase in benefit



Growing Regulatory and Patient Momentum for Patient-focused Drug Development / B-R

Regulatory (selected)



Objectives of FDA CDRH Draft Guidance on Patient Preference Information

Patient Preference Information – Submission, Review in PMAs, HDE Applications, and *De Novo* Requests, and Inclusion in Device Labeling

Draft Guidance for Industry, Food and Drug Administration Staff, and Other Stakeholders

DRAFT GUIDANCE

This guidance document is being distributed for comment purposes only.

You should submit comments and suggestions regarding this draft document within 90 days of publication in the *Federal Register* of the notice announcing the availability of the draft guidance. Submit electronic comments to <http://www.regulations.gov>. Submit written comments to the Division of Dockets Management (HFA-305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852. Identify all comments with the docket number listed in the notice of availability that publishes in the *Federal Register*.

For questions about this document, contact the Office of the Center Director (CDRH) at 301-796-5900 or Anindita Saha at 301-796-2537 (Anindita.Saha@fda.hhs.gov) or the Office of Communication, Outreach, and Development (CBER) at 800-835-4709 or 240-402-7800.



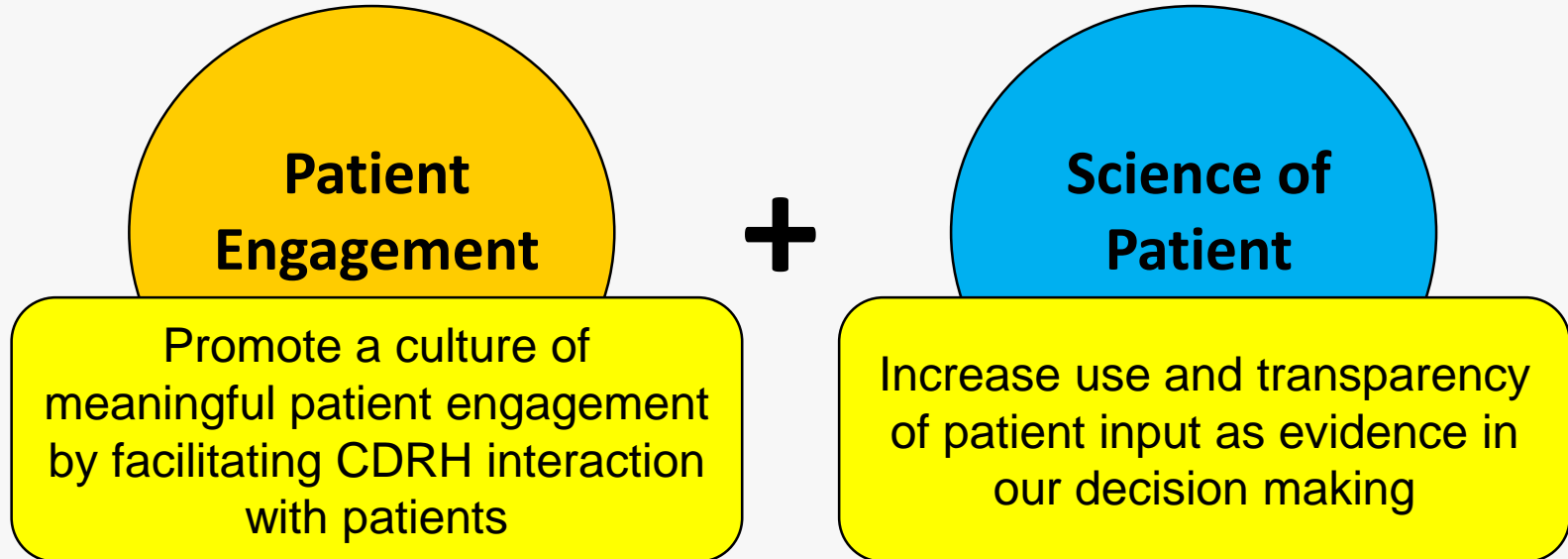
U.S. Department of Health and Human Services
Food and Drug Administration

Center for Devices and Radiological Health
Center for Biologics Evaluation and Research

- Encourage voluntary submission of patient preference information
- Provide recommendations for collecting patient preference information to FDA
- Provide recommendations for including patient preference information in labeling

CDRH Strategic Priorities 2016-2017

- Establish a National Evaluation System for medical devices
- Promote a culture of quality and organizational excellence
- **Partner with patients**



CDRH Strategic Priorities 2016-2017

- Establish a National Evaluation System for medical devices
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‘Goal: Increase use and transparency of patient input as evidence in our decision making

- By 9/30/17, 100% of ... decisions will include a public summary of available and relevant patient perspective data
- By 9/30/17, increase the number of patient perspective studies (e.g., PROs or patient preferences) used in support of ... regulatory decisions’

Growing Regulatory and Patient Momentum for Patient-focused Drug Development / B-R

Regulatory (selected)

MDIC co-founded by FDA CDRH and Industry

1Q/2013

CDHR pilot obesity pref study

4/2014

FDA CDRH draft guidance and MDIC framework on patient preferences in regulatory review and B-R

5/2015

CDRH Strategic Priorities – patient engagement

1Q/2016

FDA CDRH Patient Preference Initiative

FDA CDER Patient-focused Drug Development Meetings

2012

2013

2014

2015

2016

10/2013

PPMD policy forum on MD (19 FDA officials)

PPMD monograph on B-R in rare diseases

2Q/2014

PPMD publishes B-R preference study in Duchenne MD

PPMD submits draft guidance on Duchenne MD to FDA

11/2014

Diabetes groups/FDA forum on study endpoints

9/2014

FasterCures B-R “Boot Camp”

3Q/2015

BIO/PPMD Best Practices Toolkit for pat pref studies

4Q/2015

NHC/GA draft guidance for FDA on pat perspective in development

PDUFA VI
21st Century Cures
IMI2 PREFER Project
EMA pilot
Health Canada pilot

Patient (selected)

PPMD – Parent Project Muscular Dystrophy

BIO – Biotechnology Innovation Organization

NHC/GA – National Health Council / Genetic Alliance

Sites for MDIC Framework and FDA CDRH Draft Patient Preference Guidance



www.mdic.org/PCBR

**Patient Preference Information –
Submission, Review in PMAs, HDE
Applications, and *De Novo* Requests,
and Inclusion in Device Labeling**



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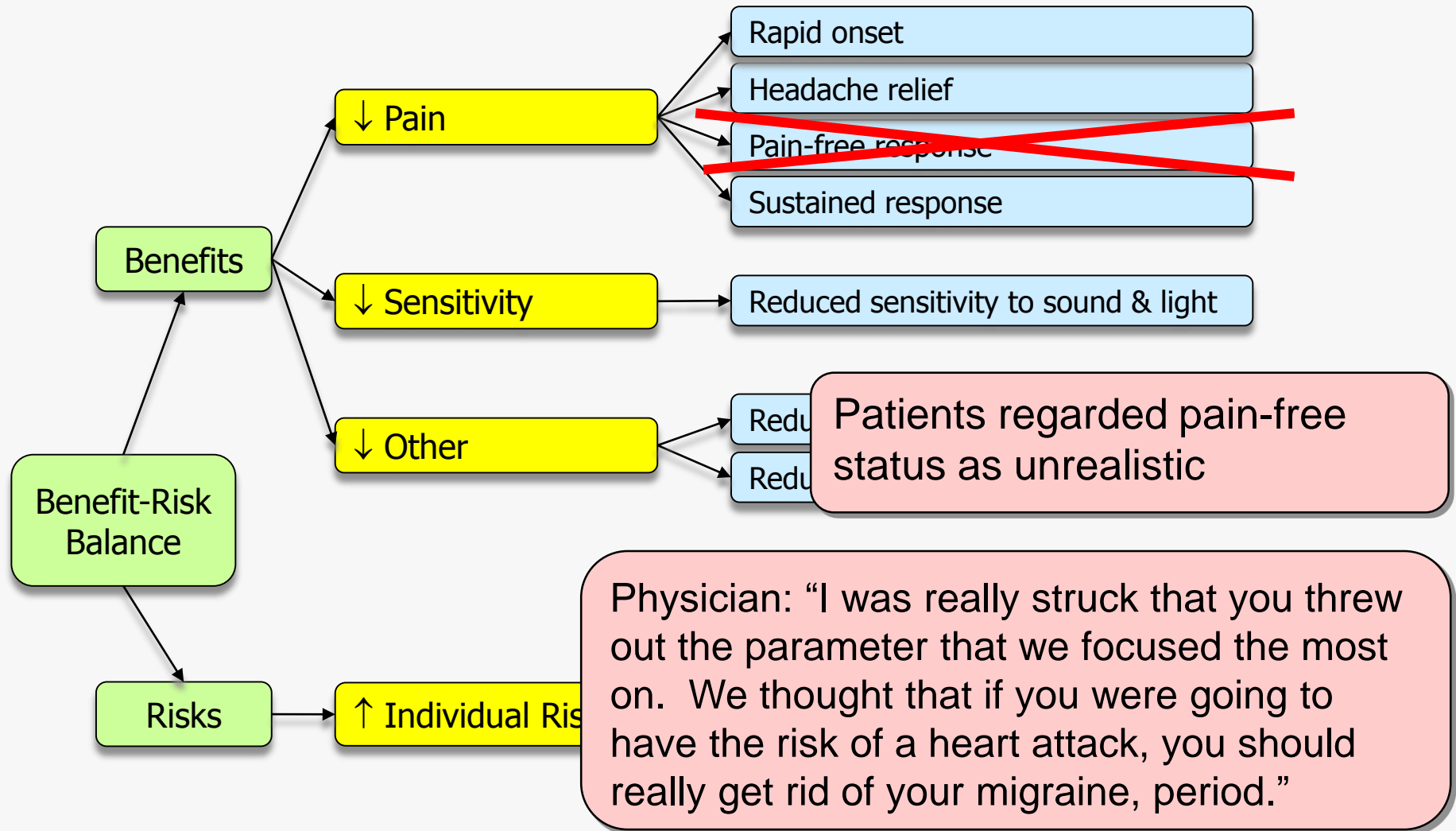
 

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Devices and Radiological Health
Center for Biologics Evaluation and Research

<http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/UCM446680.pdf>

Roles for patient preferences in regulatory review and post-approval

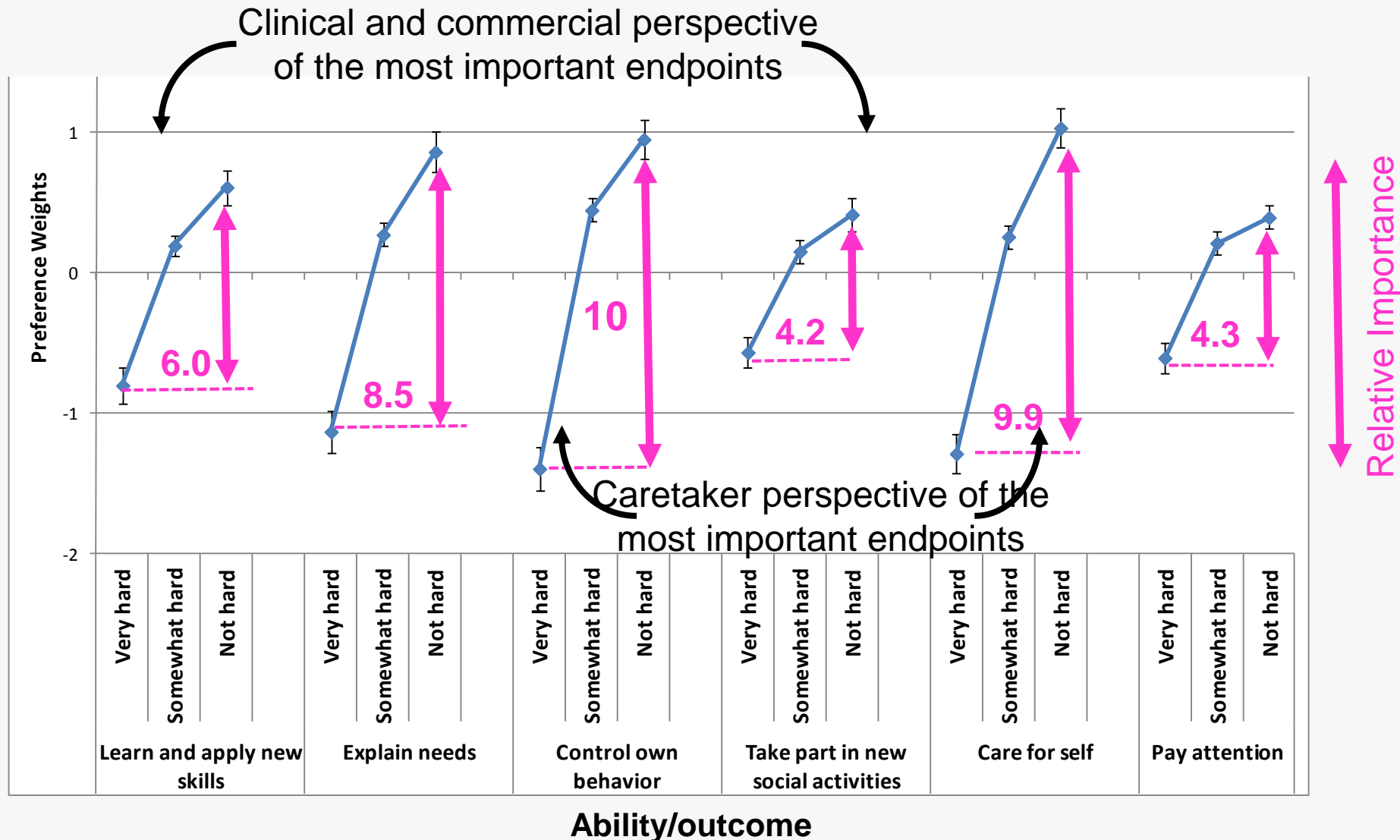
Patient Perspective: Determining Which Endpoints are Most Critical



Fragile-X Syndrome

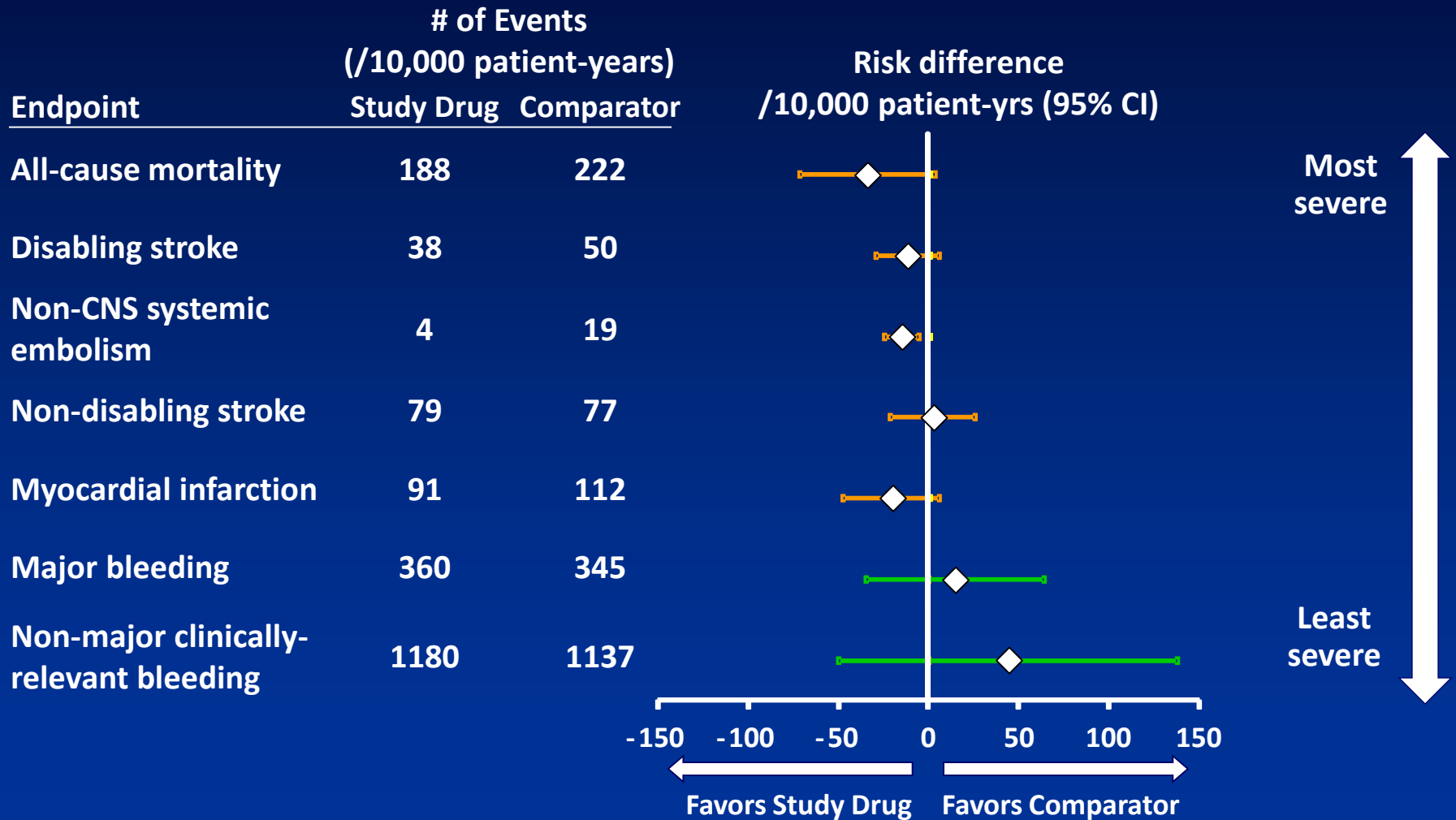
- **Rare genetic condition impacting development**
 - ▶ Learning and intellectual disabilities, cognitive impairment, behavioral challenges (ADHD, autism, social anxiety), physician features
 - ▶ No cure – educational, therapeutic support
- **Preference study conducted to prepare for phase 3 study**
 - ▶ No established endpoints or effect sizes
 - ▶ Intent was to identify which endpoints or components of existing instruments were most important to patients
 - ▶ Survey administered to family members, given patient cognitive limitations

Preference Survey Identified Large Gap Between Clinician and Patient Caretaker Beliefs on Endpoint Importance



Risk Differences by Clinical Severity/Impact[†]

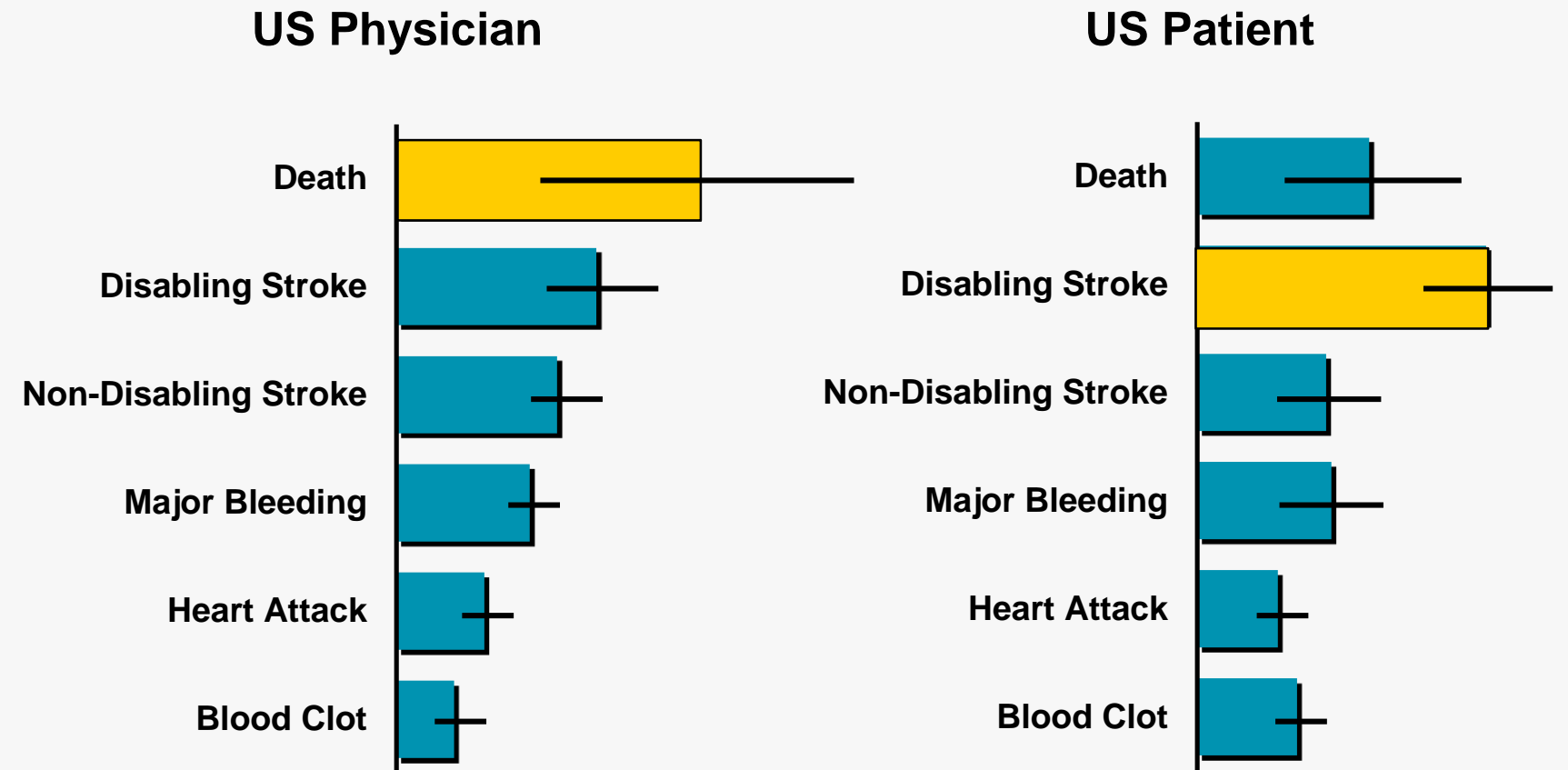
Atrial Fibrillation Example



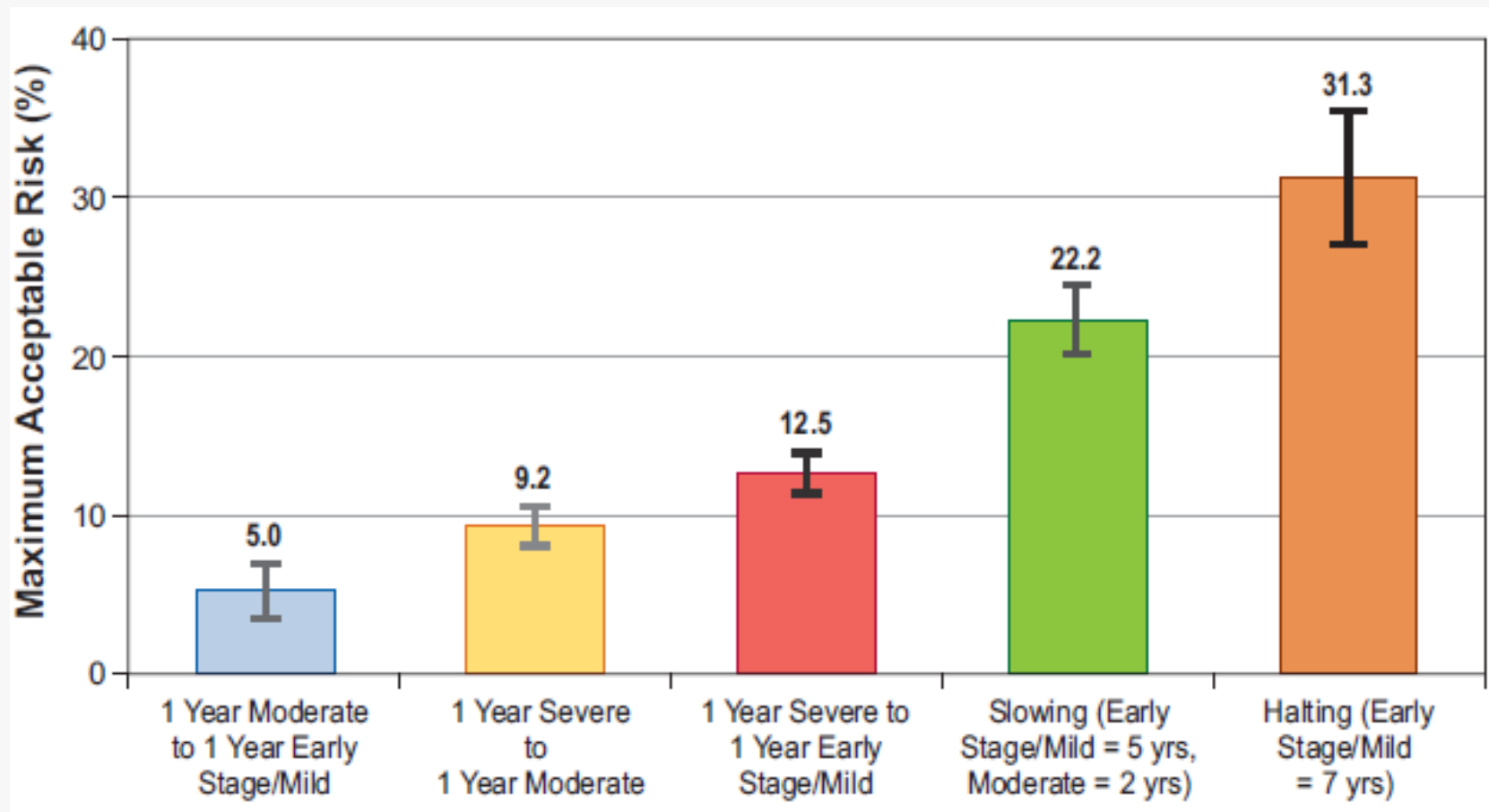
[†] Endpoints in order of health state utility, a value that reflects preference for health states relative to perfect health and death.

Identifying Differences Between Key Stakeholders

Preferences for Anticoagulants in Atrial Fibrillation



Maximum Acceptable Risk of treatment-related death or permanent severe disability due to stroke



Hauber AB, Johnson FR, Fillit H, et al. Older Americans' risk-benefit preferences for modifying the course of Alzheimer disease. *Alzheimer Dis Assoc Disord.* Jan-Mar 2009;23(1):23-32

A Key Idea

To use patient viewpoints in a regulatory context requires more than expressions of feelings or opinions – it needs defensible **data**

Preference studies have the potential to obtain these data reliably

A Goal

Endpoint	Study Drug/ 10,000 pt-yrs	Comparator Rate/ 10,000 pt-yrs	HR (95% CI)	Risk Difference / 10,000 pt-yrs
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