Patient-focused Benefit-Risk Assessment

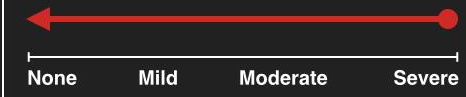
March 4, 2016

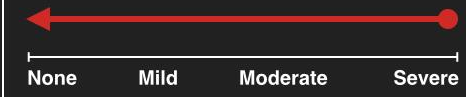
NIH HCS Collaboratory and PCORnet Grand Rounds

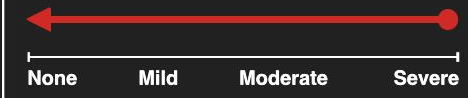
Bennett Levitan, MD-PhD

Department of Epidemiology

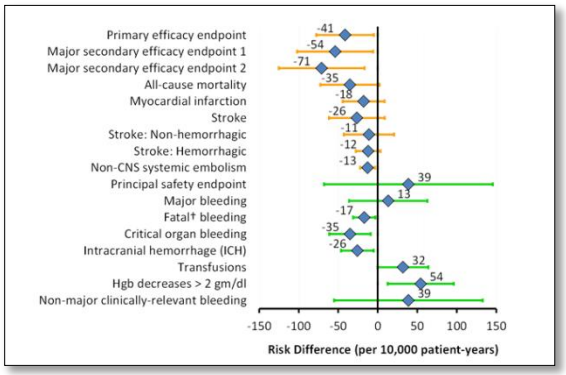
Janssen Research & Development, LLC

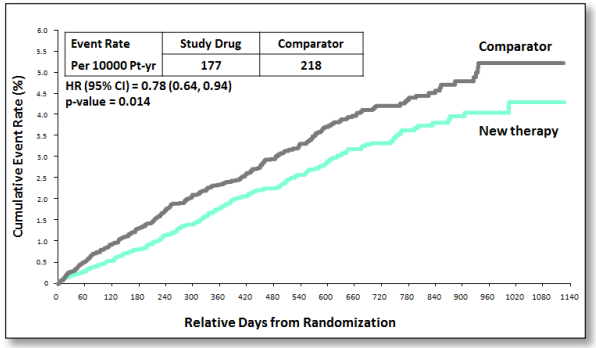
Outcome	Drug A	Drug B
Relief of pain		
Ability to perform work/school and social activities	No limitations	Cannot work, difficulty with chores and shopping
Annual chance of a heart attack	1 in 10,000	No chance
Which medicine would you choose if these were the only medicines available?	☐	☐

Outcome	Drug C	Drug B
Relief of pain		
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?	☐	☐

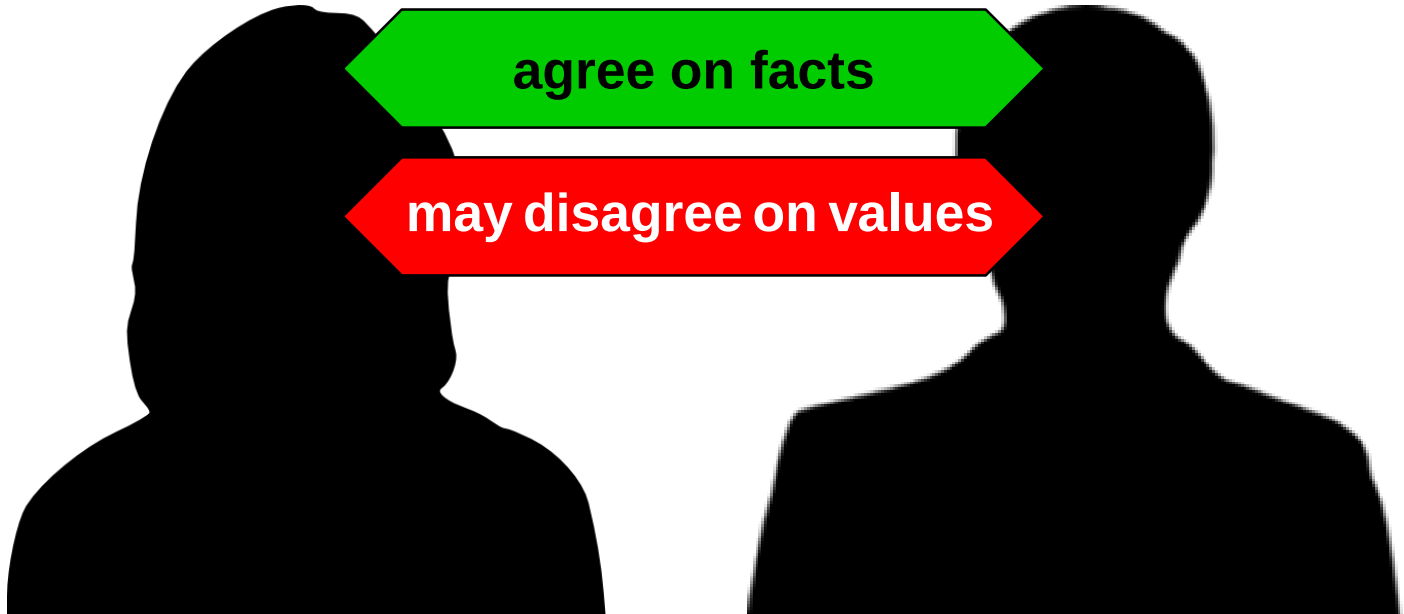
Outcome	Drug D	Drug B
Relief of pain		
Ability to perform work/school and social activities	No limitations	Cannot work, difficulty with chores and shopping
Annual chance of a heart attack	1 in 100	No chance
Which medicine would you choose if these were the only medicines available?	☐	☐

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

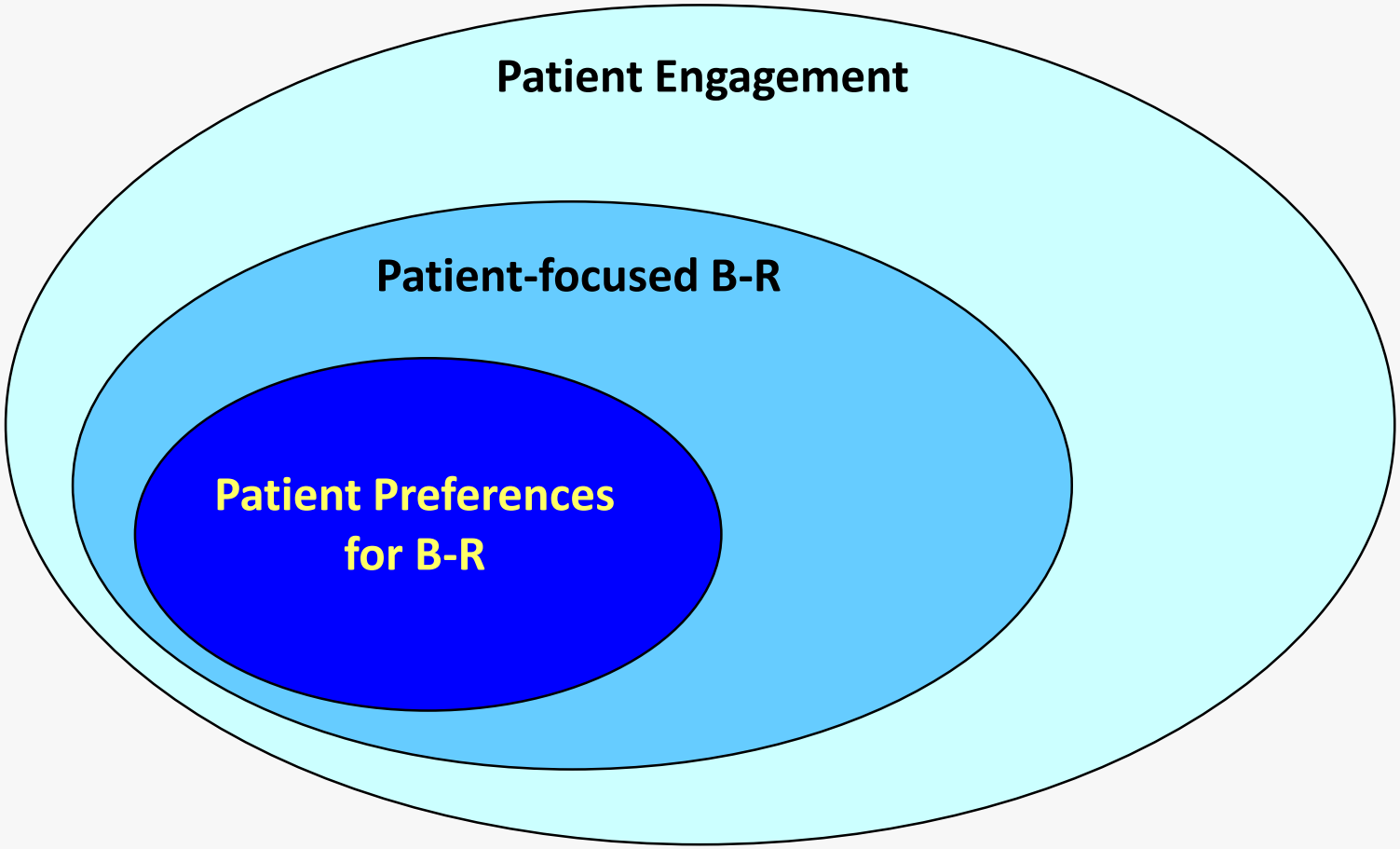
- **Patients would accept up to a 2/1000 (95% CI 1.6 – 2.4) annual heart attack risk in exchange for restoring their ability to function during migraines**

Gonzalez, Hauber, Levitan, Coplan, ISPOR 17th Annual International Meeting June, 2012.

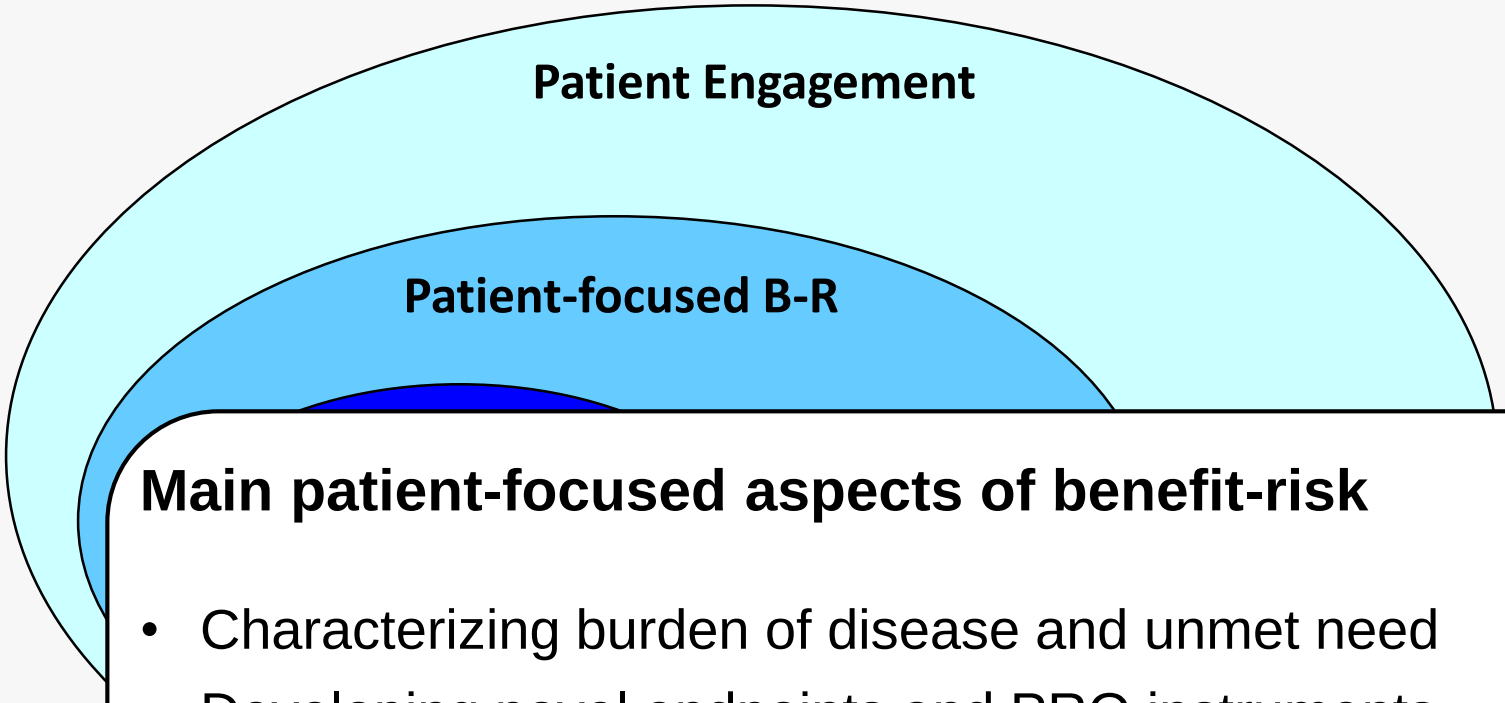
Benefit-risk Assessment

- **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



Main patient-focused aspects of benefit-risk

- Characterizing burden of disease and unmet need
- Developing novel endpoints and PRO instruments
- Determining which endpoints/rates/levels are most important
- Assessing preference tradeoffs between endpoints
- Identifying preference heterogeneity and subgroups

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

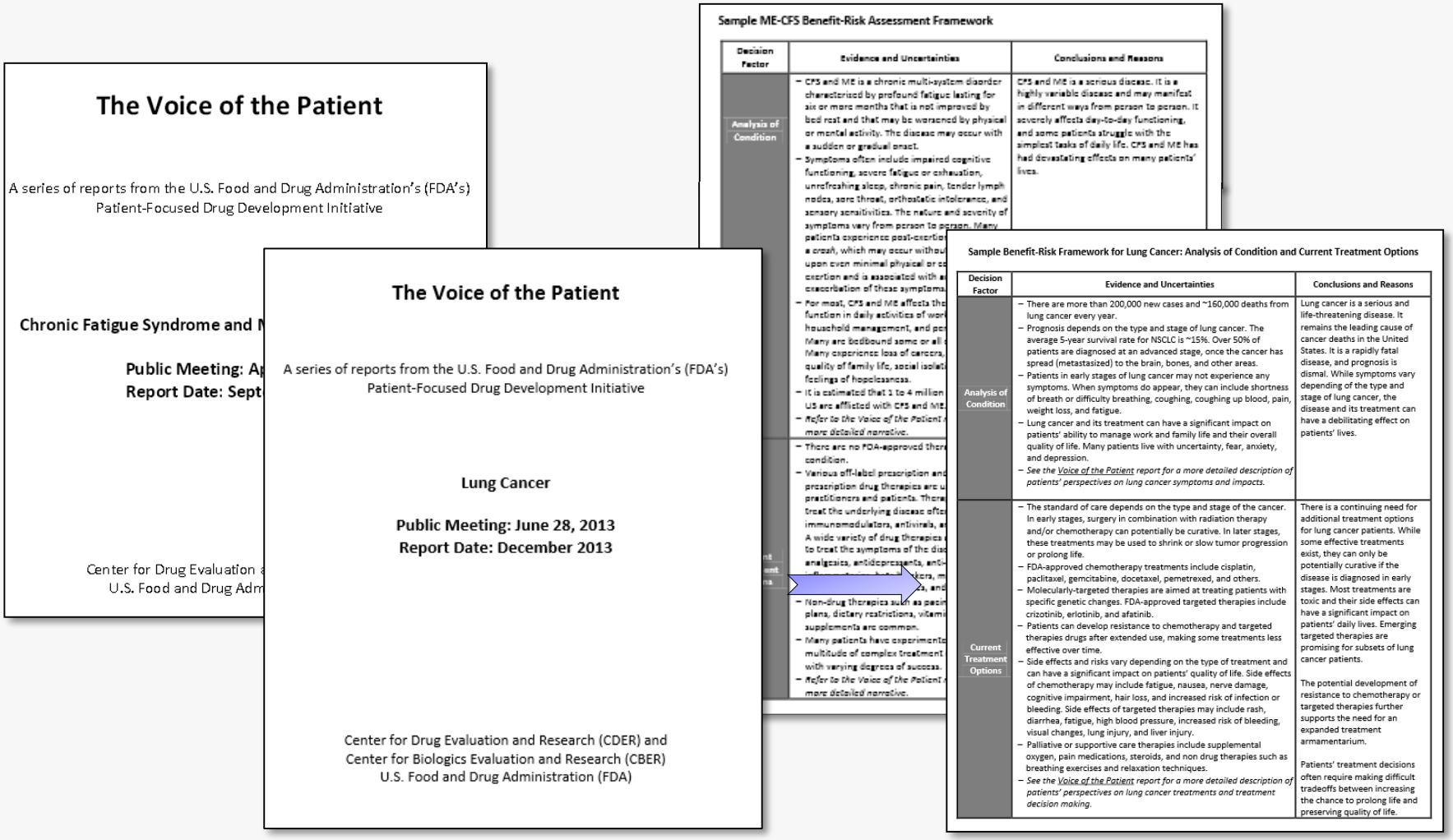
Regulatory (selected)

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		

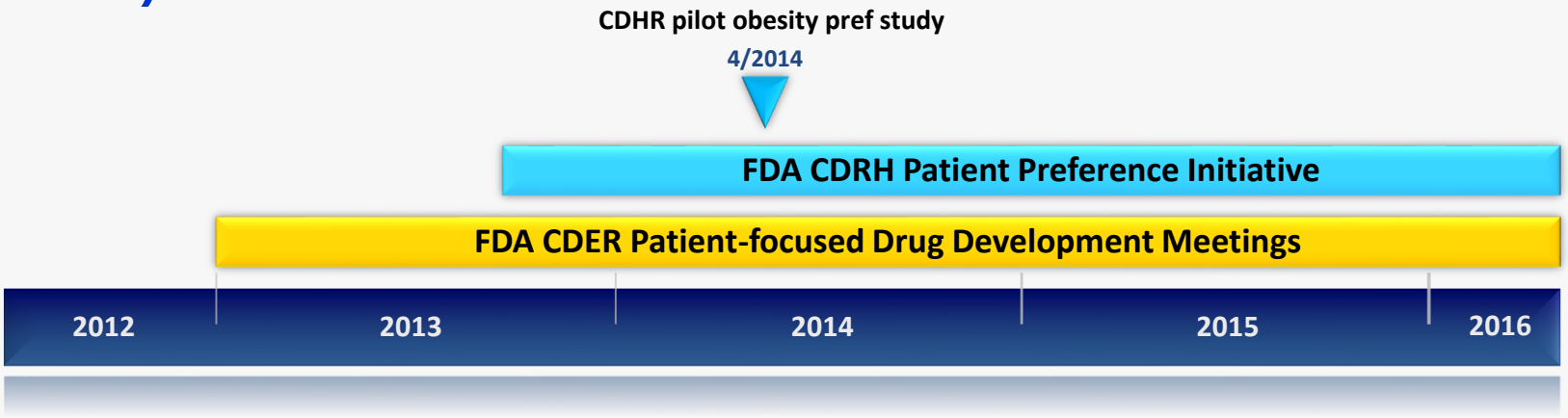
FDA's "Voice of the Patient" Report Series
Patient views become part of B-R Framework

FDA B-R Framework

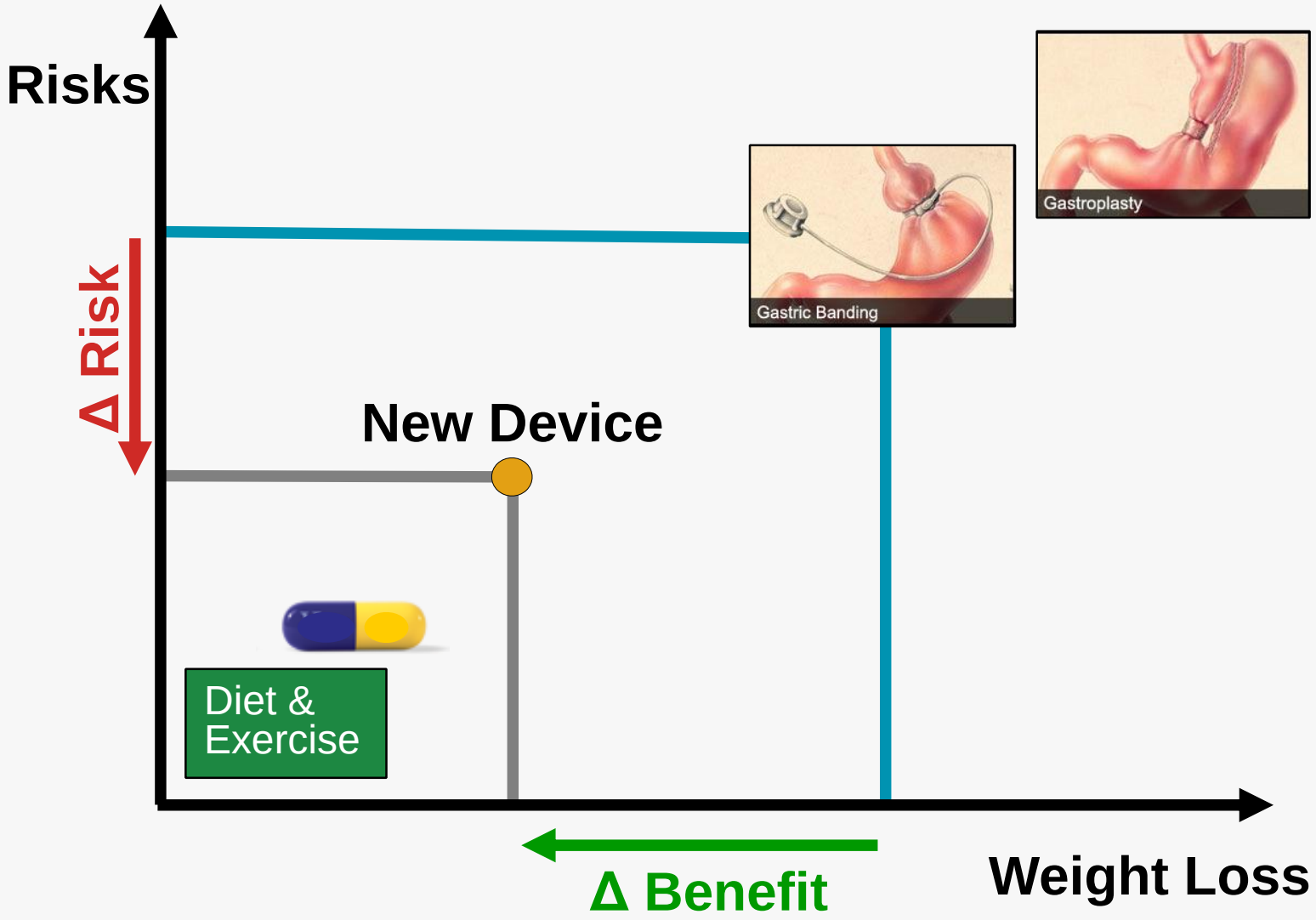


Growing Regulatory and Patient Momentum for Patient-focused Drug Development / B-R

Regulatory (selected)



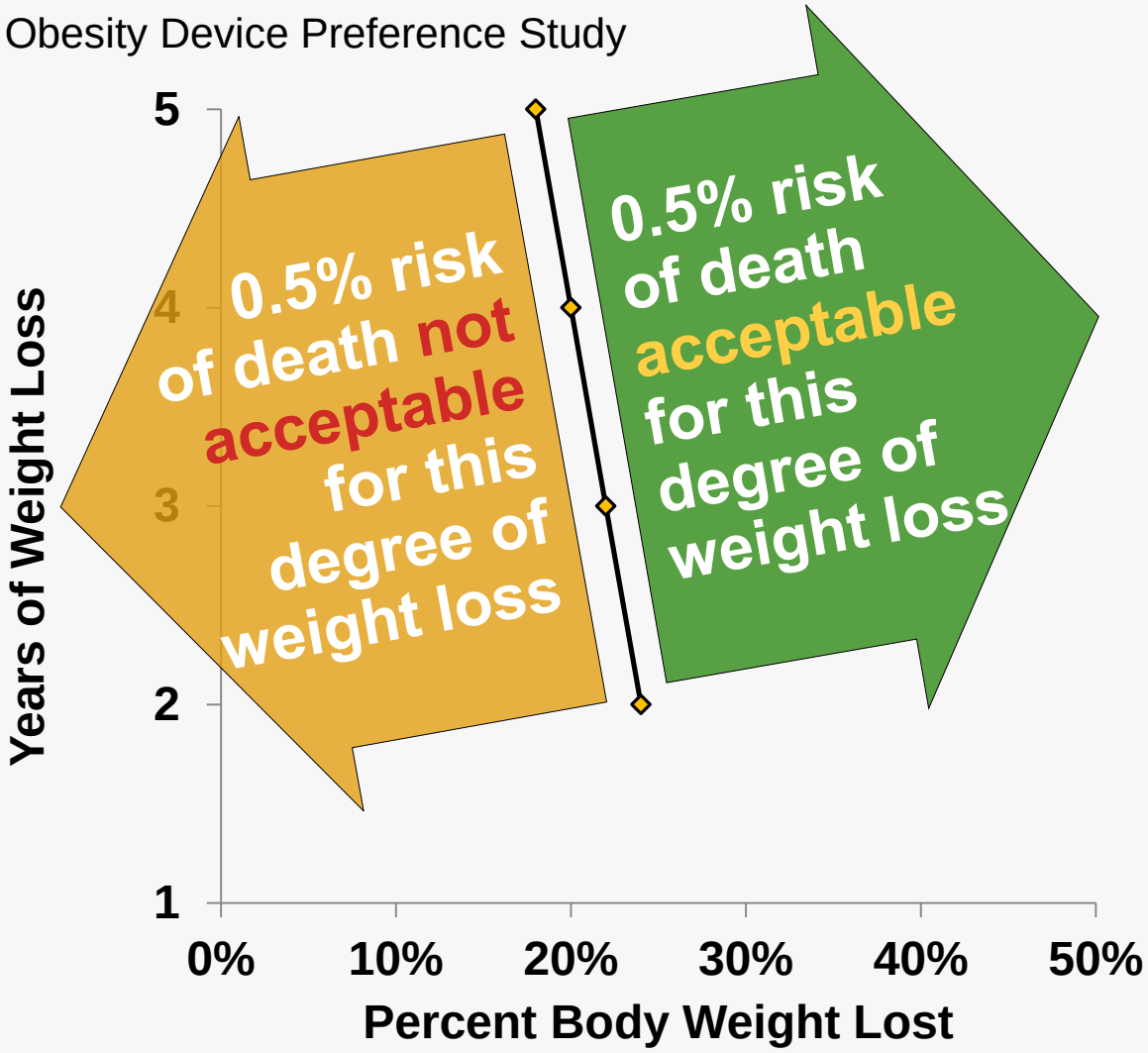
FDA CDRH Obesity Device Preference Study



Ho, M. P., et al. (2015). "Incorporating patient-preference evidence into regulatory decision making." Surg Endosc.

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

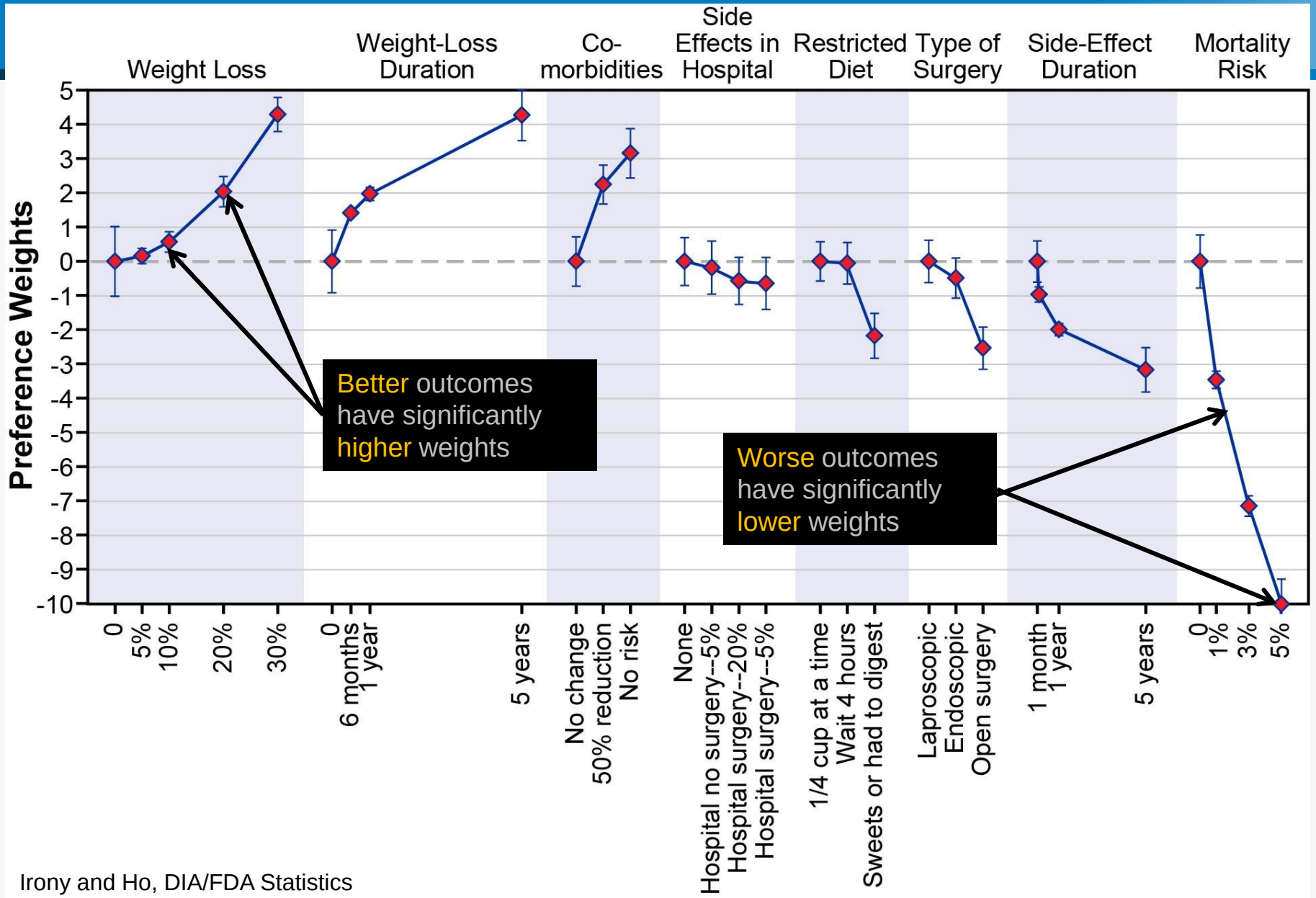
FDA CDRH/RTI Obesity Device Preference Study



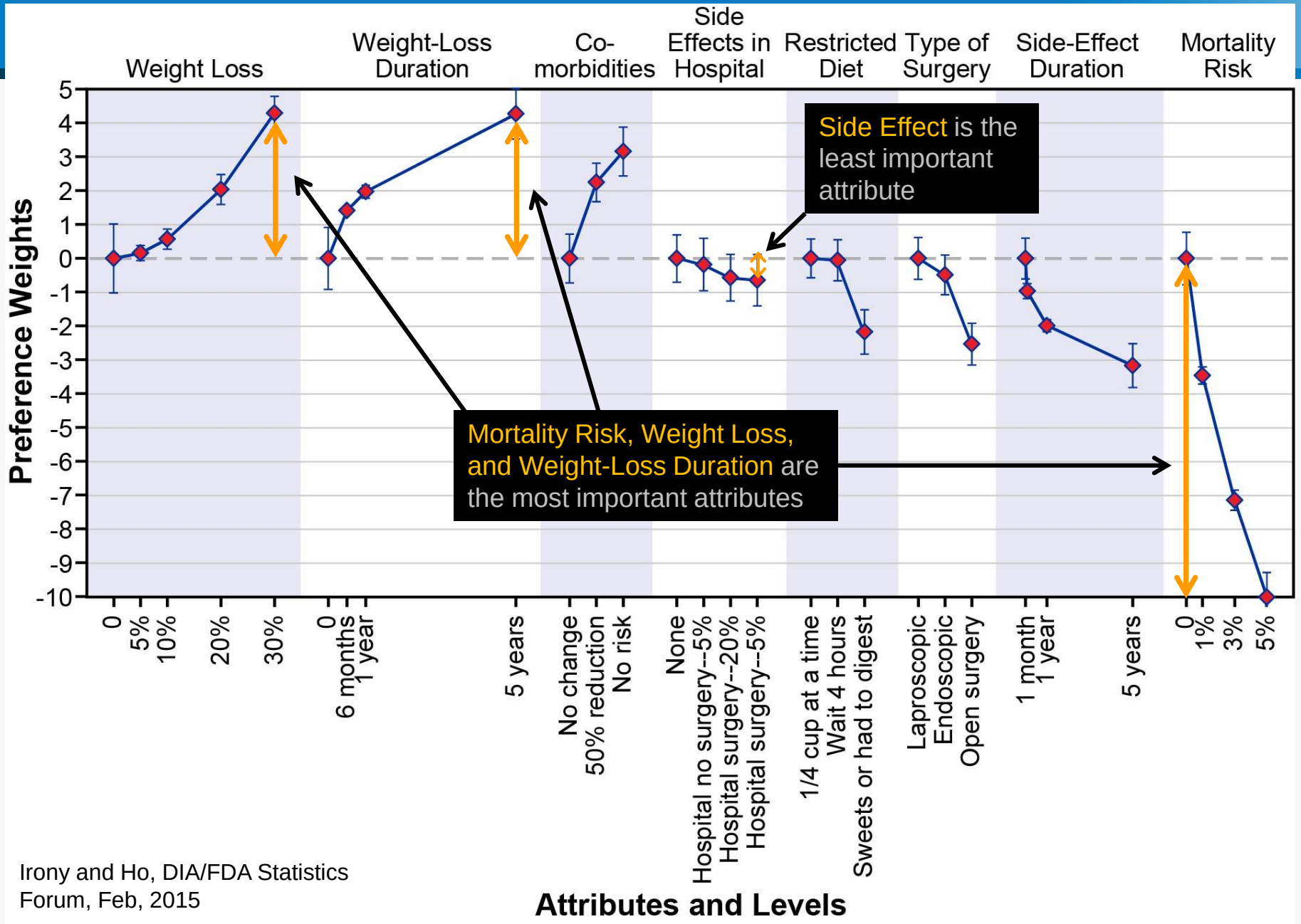
Irony and Ho, DIA/FDA Statistics Forum, Feb, 2015

Results for average obese patient (243lbs and 5'10")

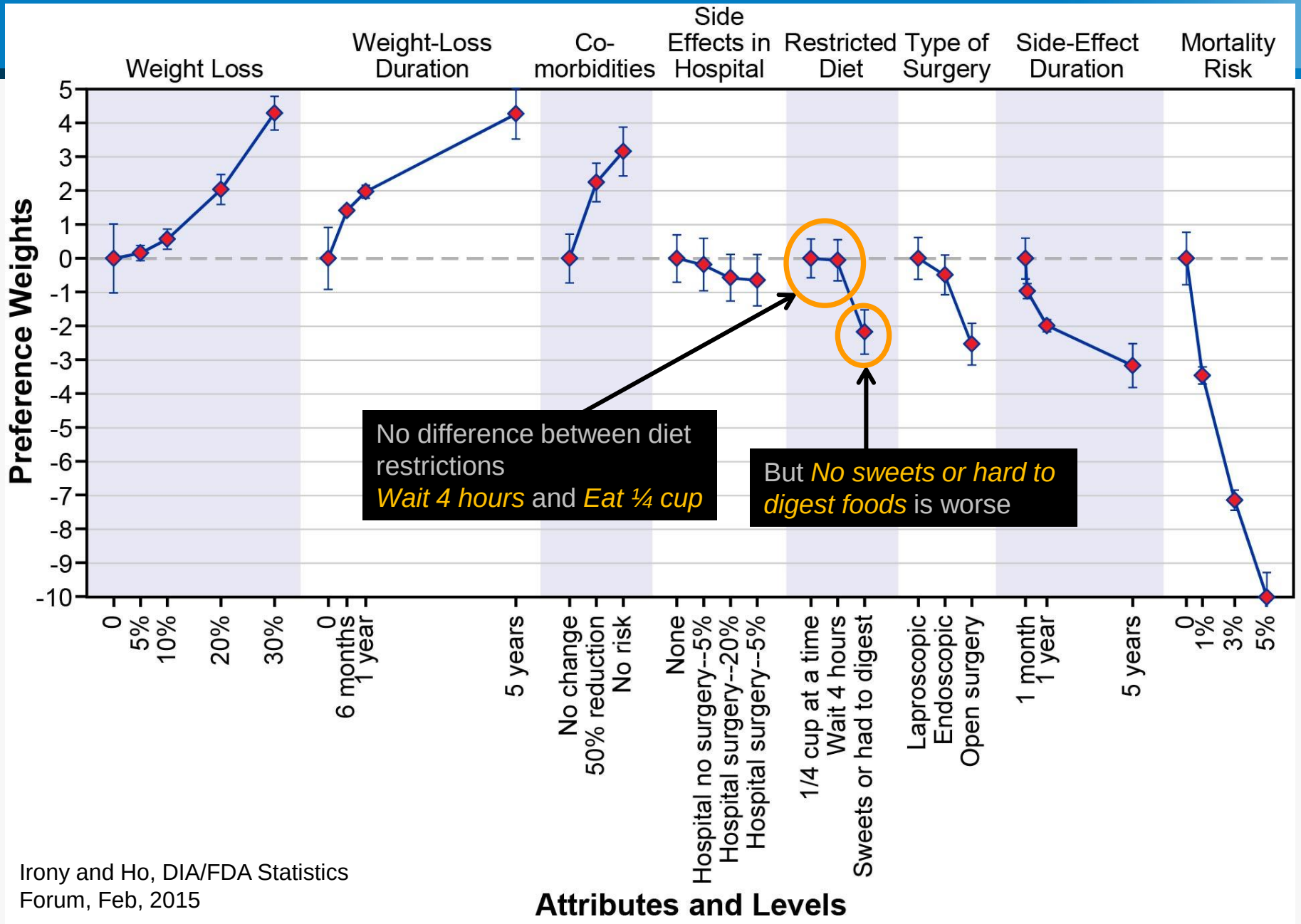
Mean Preference Weights



Mean Preference Weights



Mean Preference Weights



Irony and Ho, DIA/FDA Statistics Forum, Feb, 2015

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

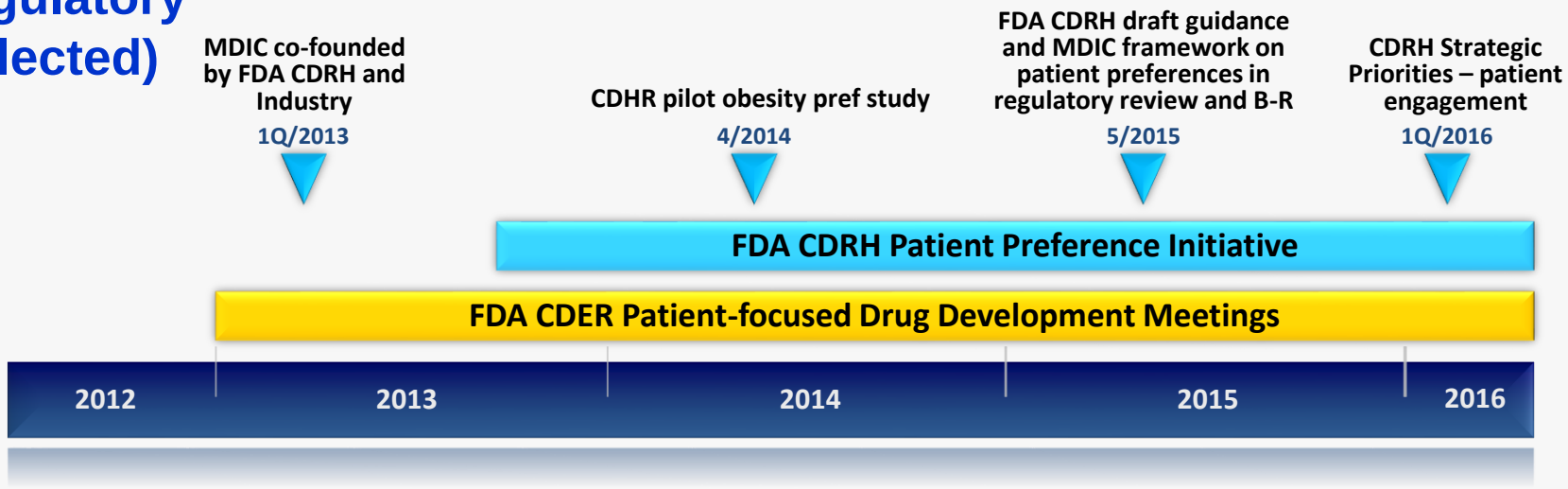
The agency approved EnteroMedics' *Maestro* neuromodulator to treat obesity despite the device not meeting endpoints in its pivotal trial. The agency relied in part on a survey that found obese patients willing to take more risks in exchange for weight loss.

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.

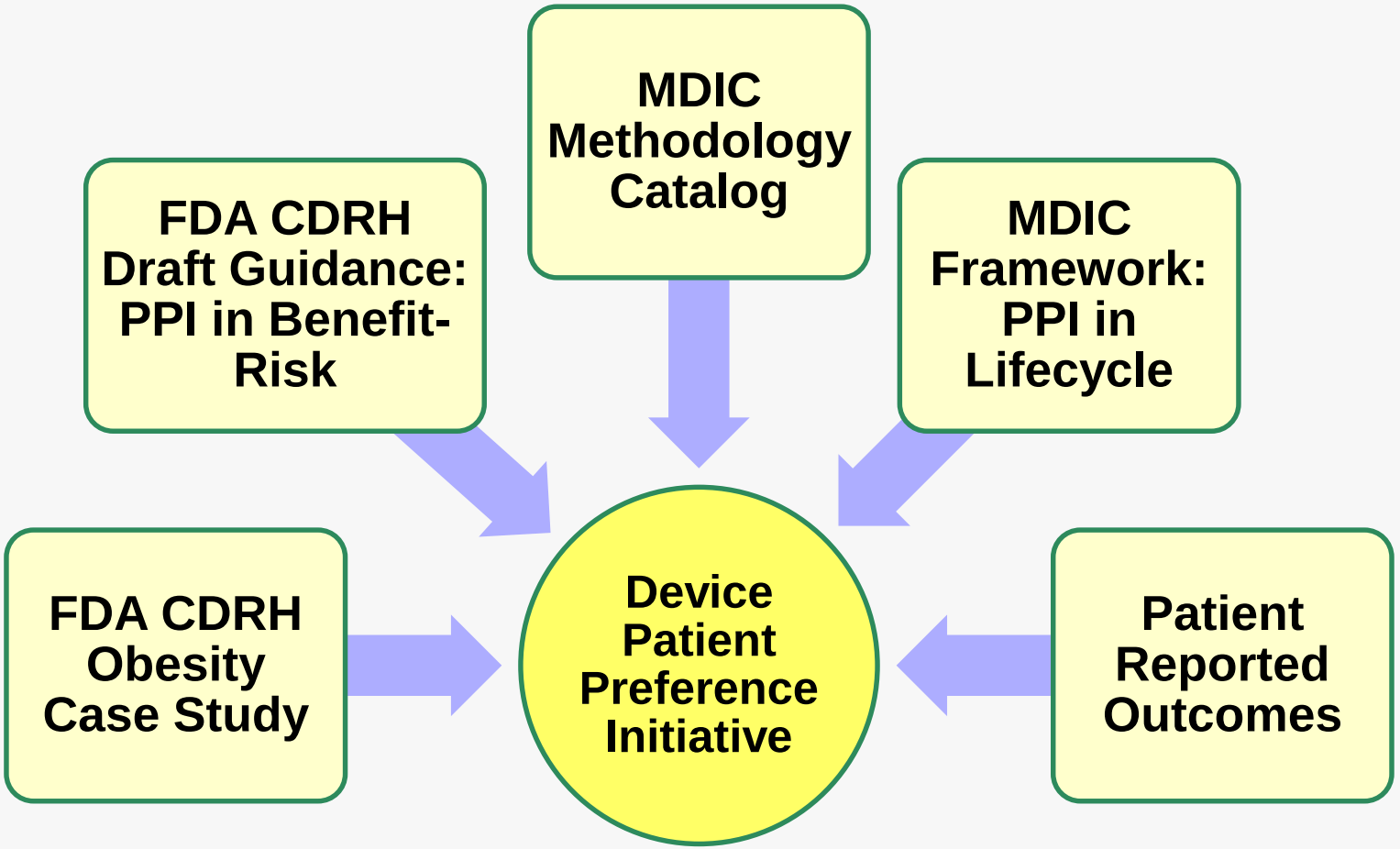
Pink Sheet 1/20/15

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

Regulatory (selected)



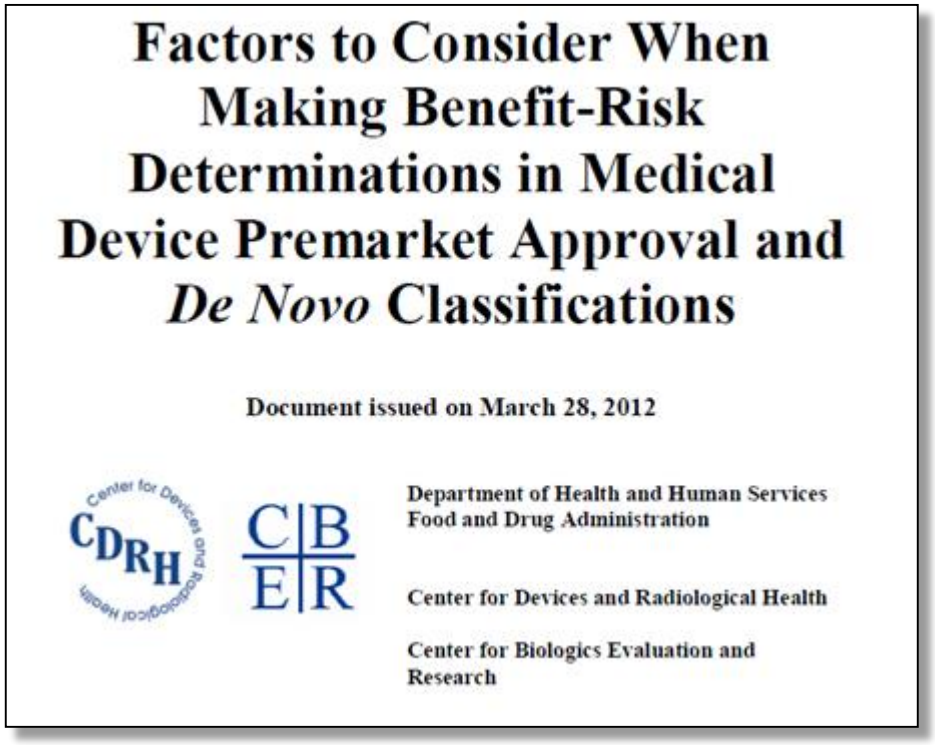
FDA CDRH Patient Preference Initiative: Collaborative Building Blocks



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…

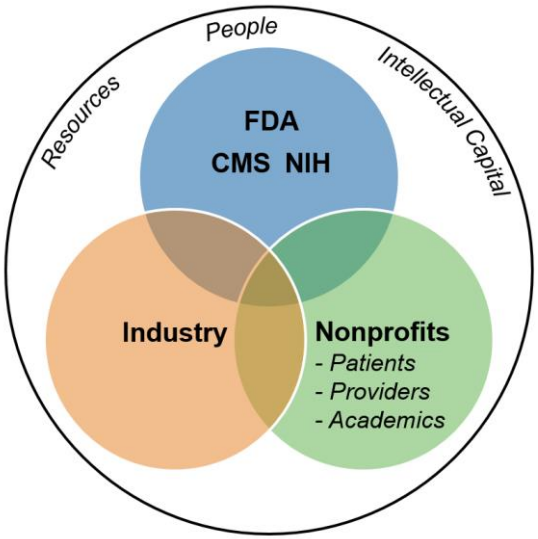
Medical Device Innovation Consortium

- **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

MDIC
MEDICAL DEVICE INNOVATION CONSORTIUM



Align Resources

Accelerate Progress

Achieve Results

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

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

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

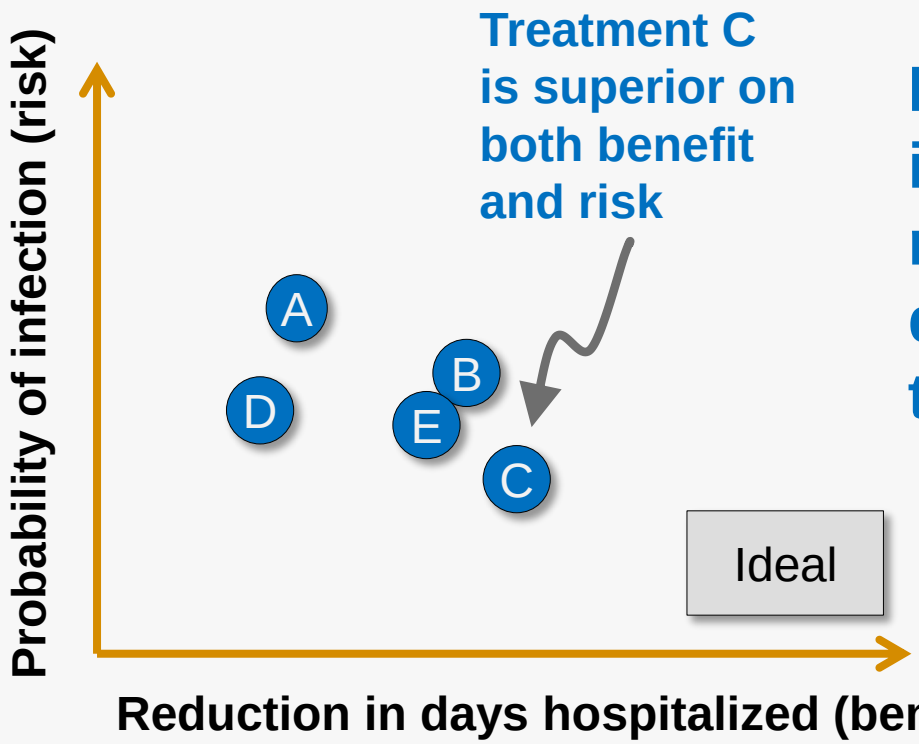
What are “Preferences”?

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.

Medical Device Innovation Consortium Patient-centered Benefit-risk Framework, http://mdic.org/wp-content/uploads/2015/05/MDIC_PCBR_Framework_Web.pdf

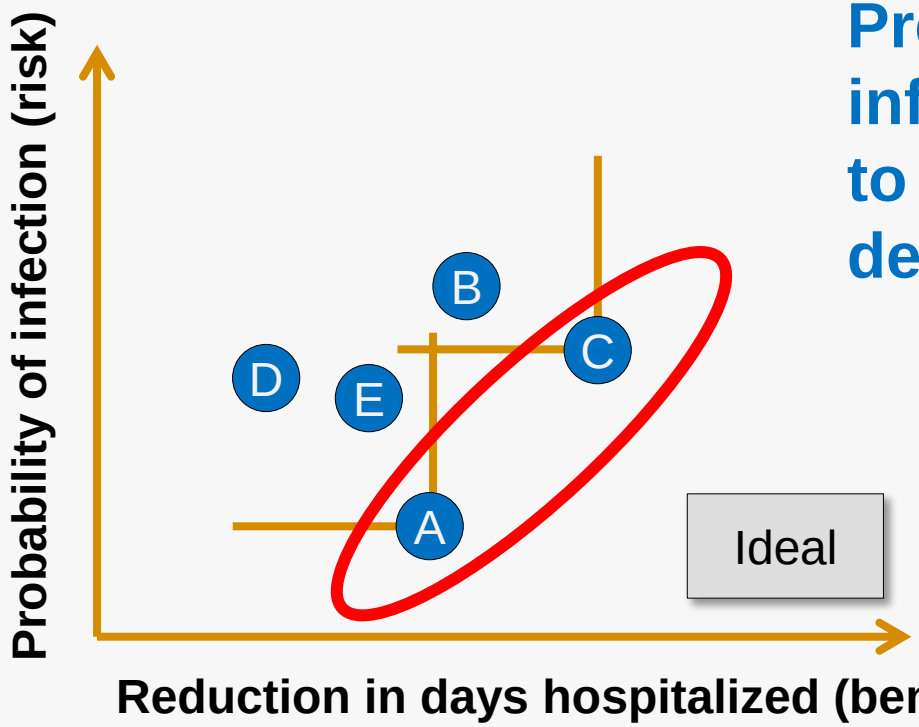
Which Treatment is Best?



Preference information is not needed to determine the best treatment

Medical Device Innovation Consortium Patient-centered Benefit-risk Framework, http://mdic.org/wp-content/uploads/2015/05/MDIC_PCBR_Framework_Web.pdf

Now Which Treatment is Best?

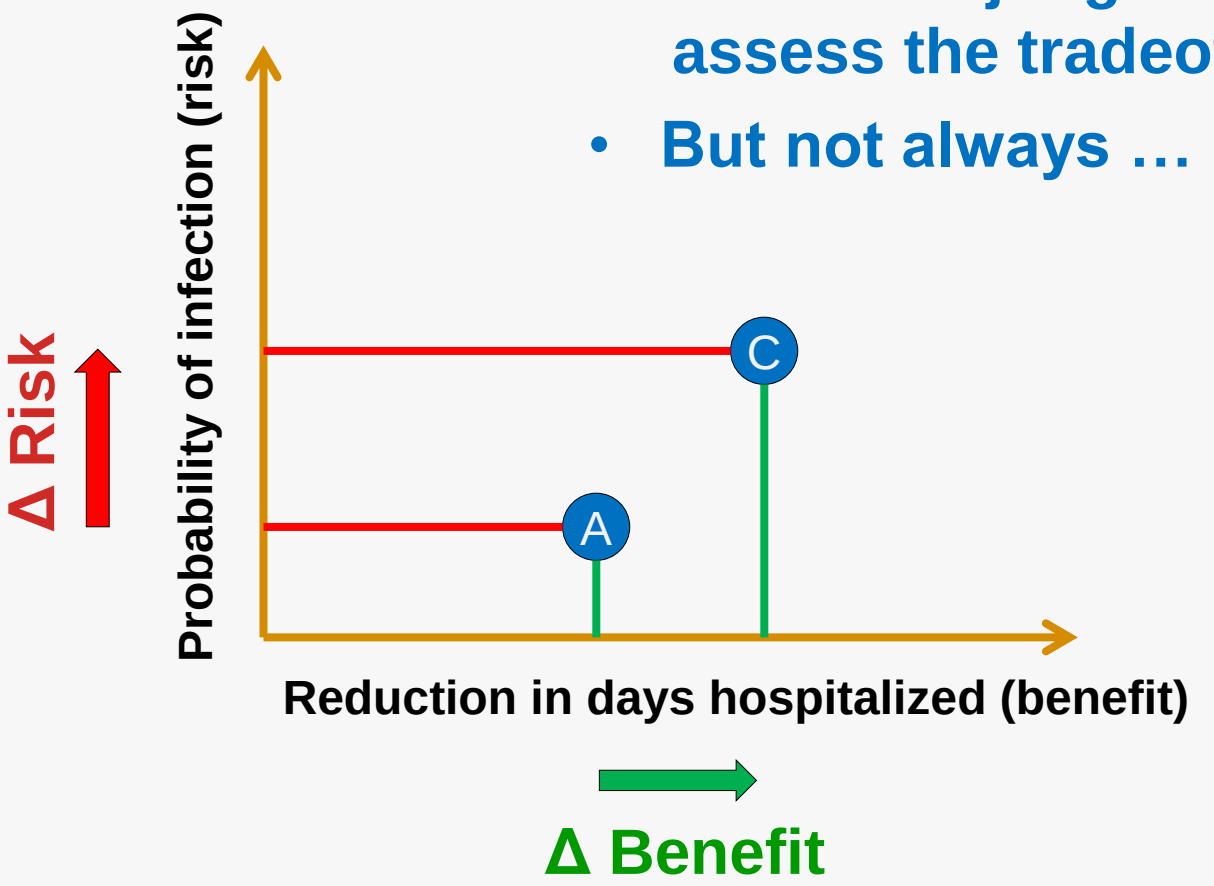


Preference information is needed to choose between devices A and Cs

This is a "Preference Sensitive Decision"

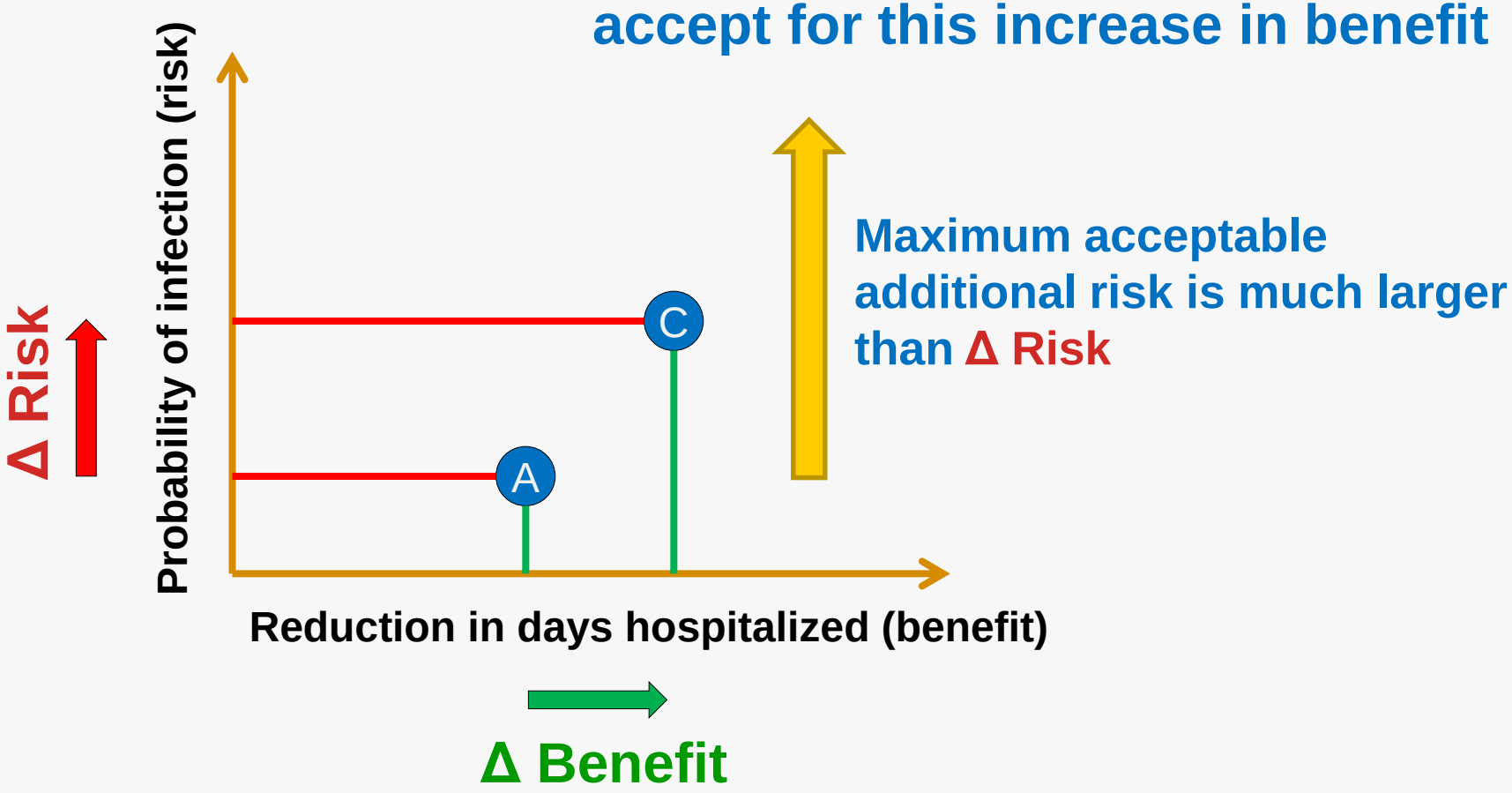
How Do Preferences Help Us Choose?

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



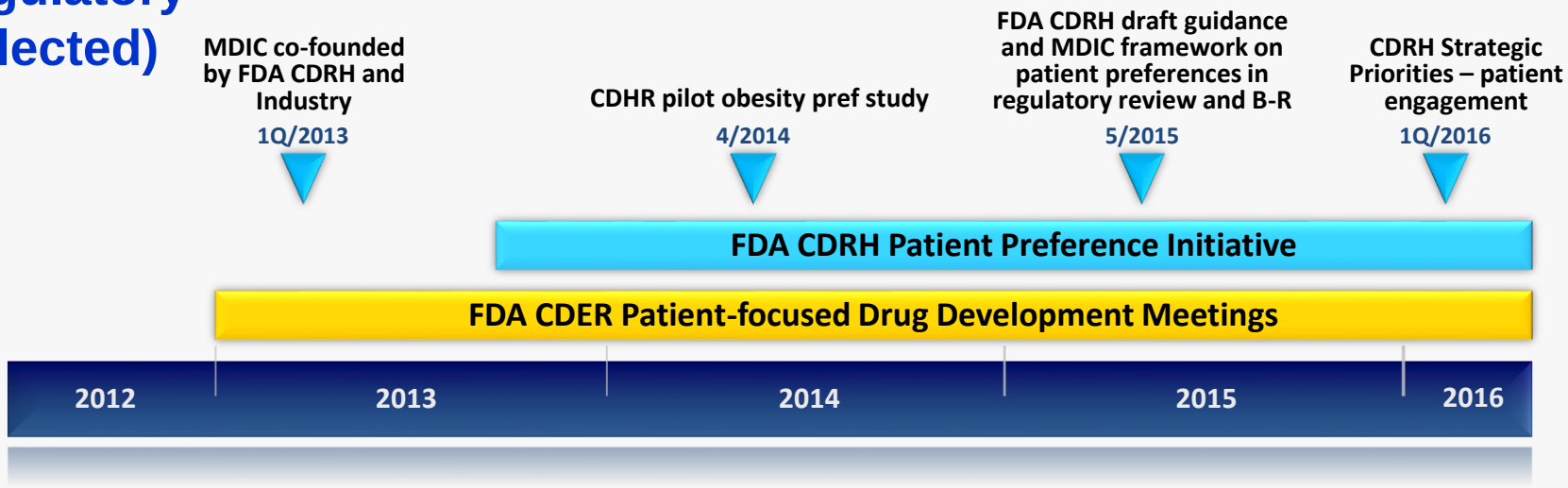
How Do Preferences Help Us Choose?

- **Preference studies give the maximum additional risk that <u>patients</u> would accept for this increase in benefit**

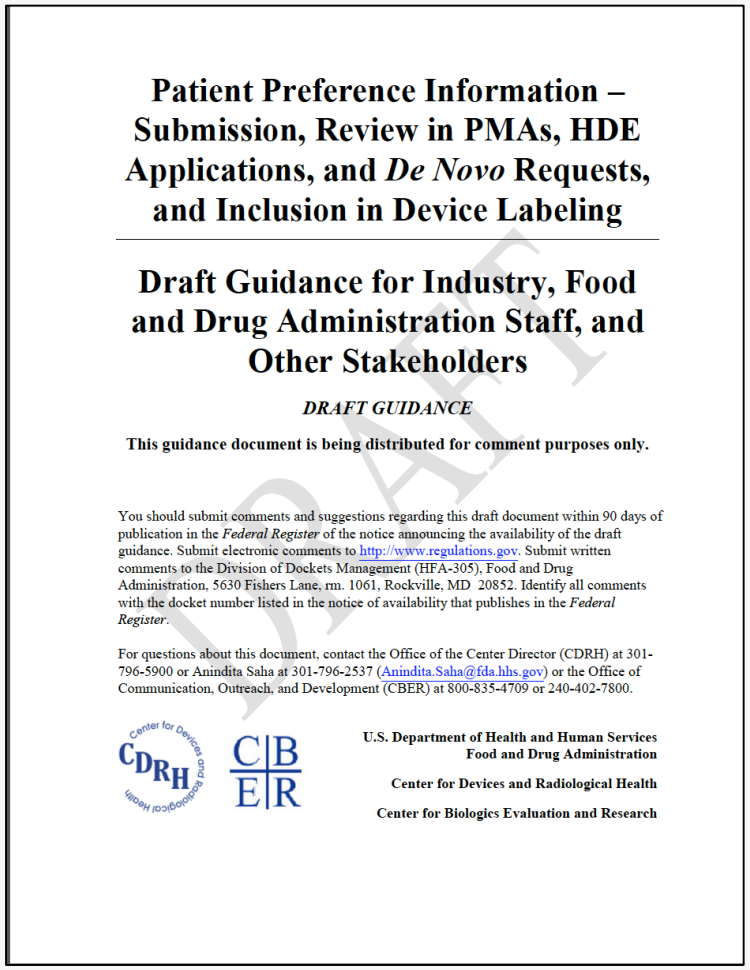


Growing Regulatory and Patient Momentum for Patient-focused Drug Development / B-R

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.

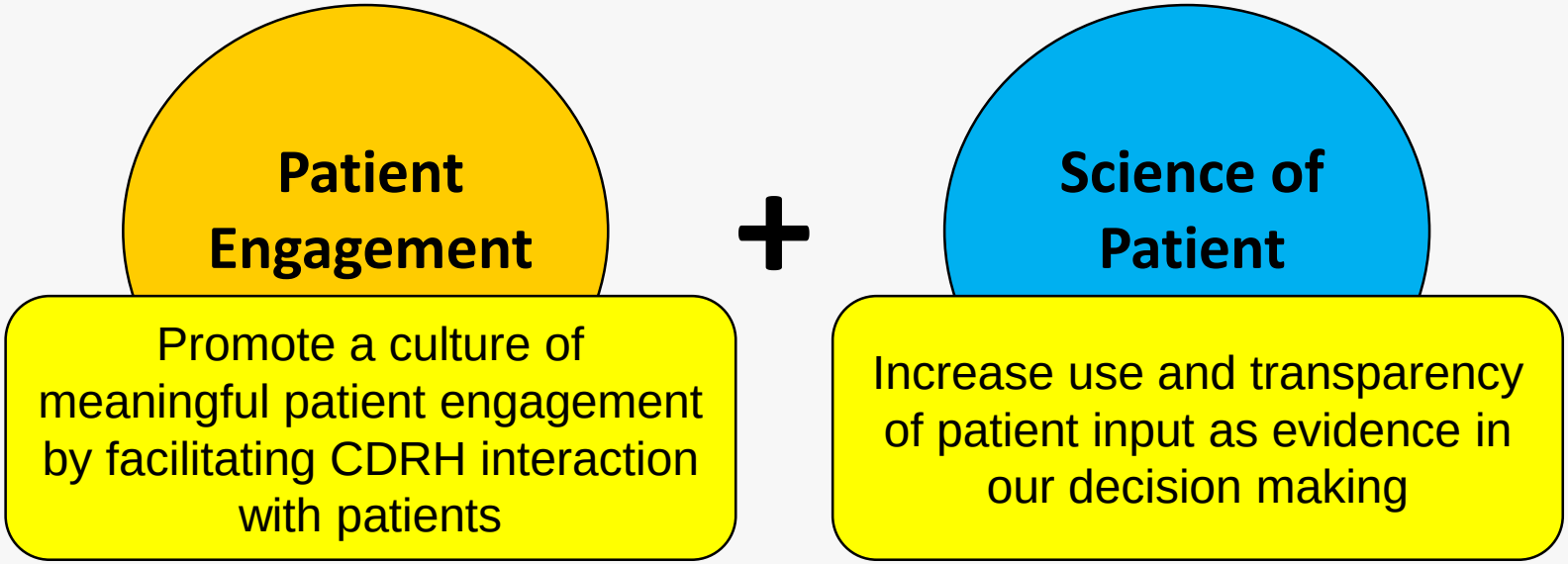
U.S. Department of Health and Human Services
Food and Drug Administration
Center for Devices and Radiological Health
Center for Biologics Evaluation and Research

DRAFT

- **<u>Encourage voluntary submission</u> of patient preference information**
- **Provide recommendations for collecting patient preference information to FDA**
- **Provide recommendations for <u>including patient preference information in labeling</u>**

CDRH Strategic Priorities 2016-2017

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



www.fda.gov/downloads/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDRH/CDRHVisionandMission/UCM481588.pdf

CDRH Strategic Priorities 2016-2017

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

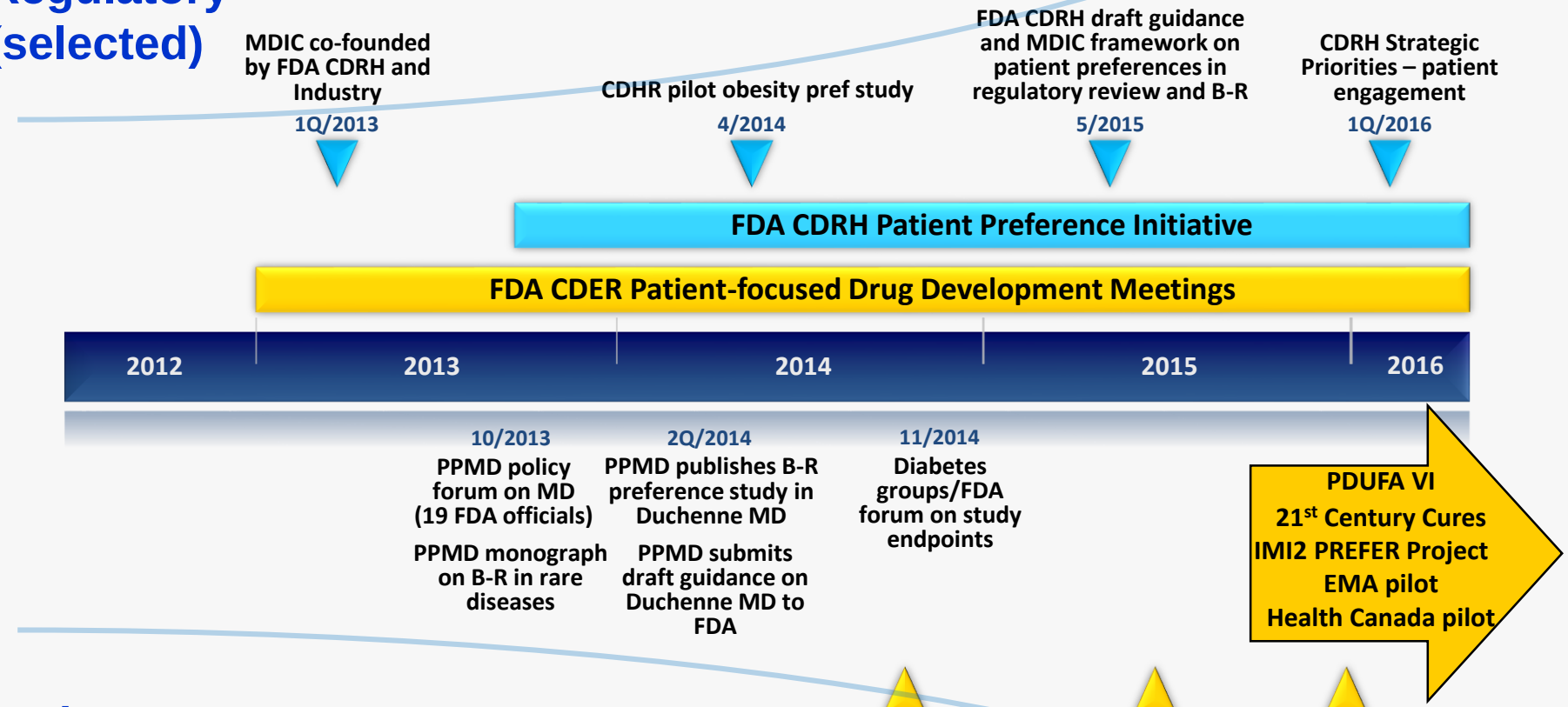
'Goal: Increase use and transparency of patient input as evidence in our decision making

- 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'

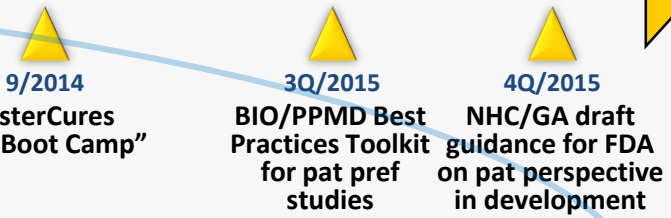
www.fda.gov/downloads/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDRH/CDRHVisionandMission/UCM481588.pdf

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

Regulatory (selected)



Patient (selected)

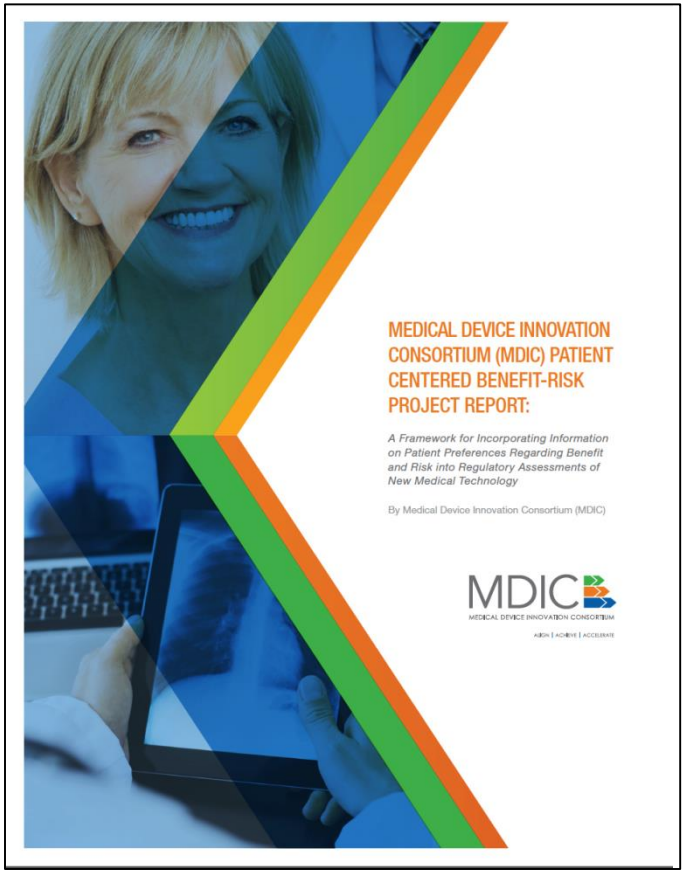


PPMD – Parent Project Muscular Dystrophy

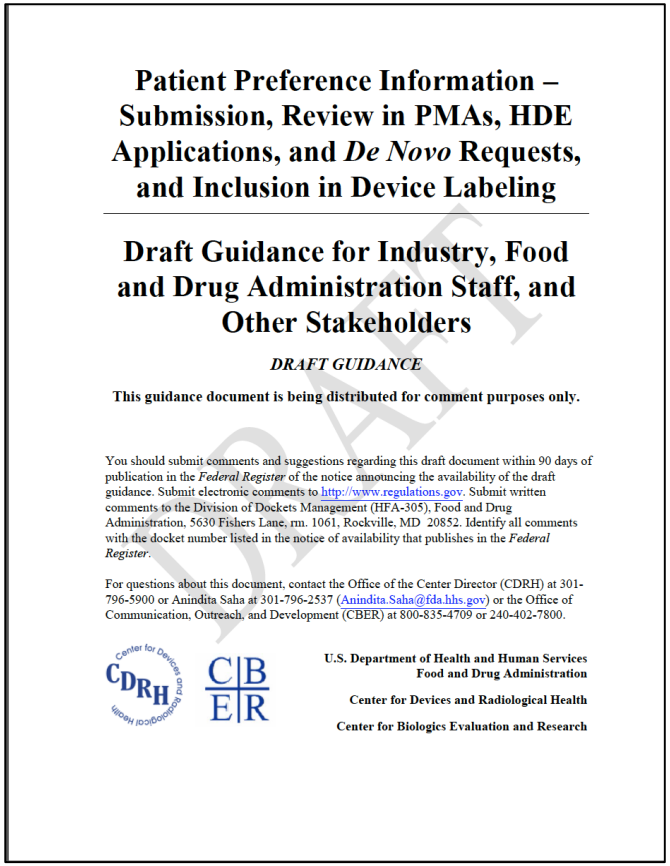
BIO – Biotechnology Innovation Organization

NHC/GA – National Health Council / Genetic Alliancde

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

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.

CDRH Center for Devices and Radiological Health

CBER

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

Center for Devices and Radiological Health

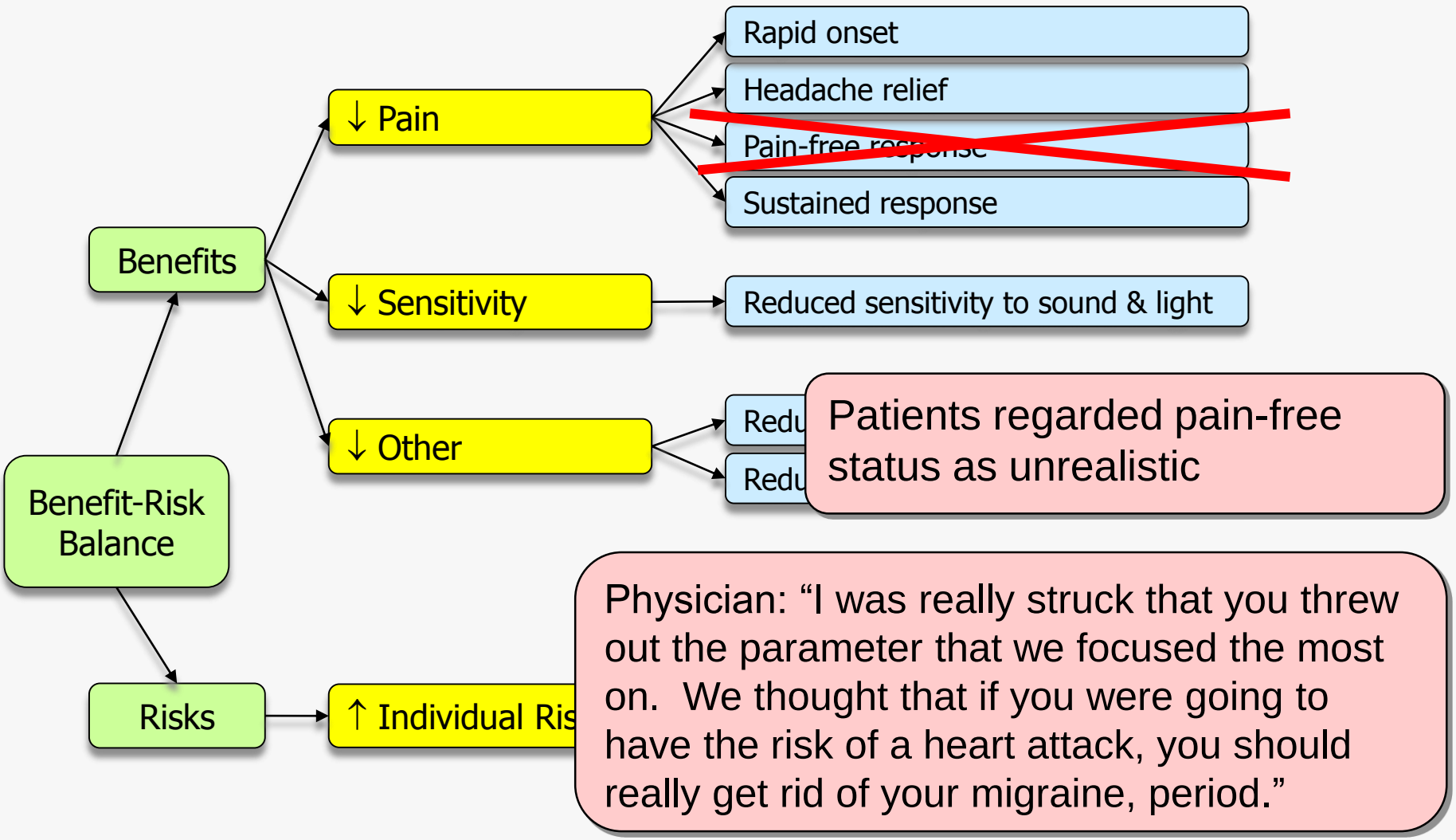
Center for Biologics Evaluation and Research

DRAFT

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

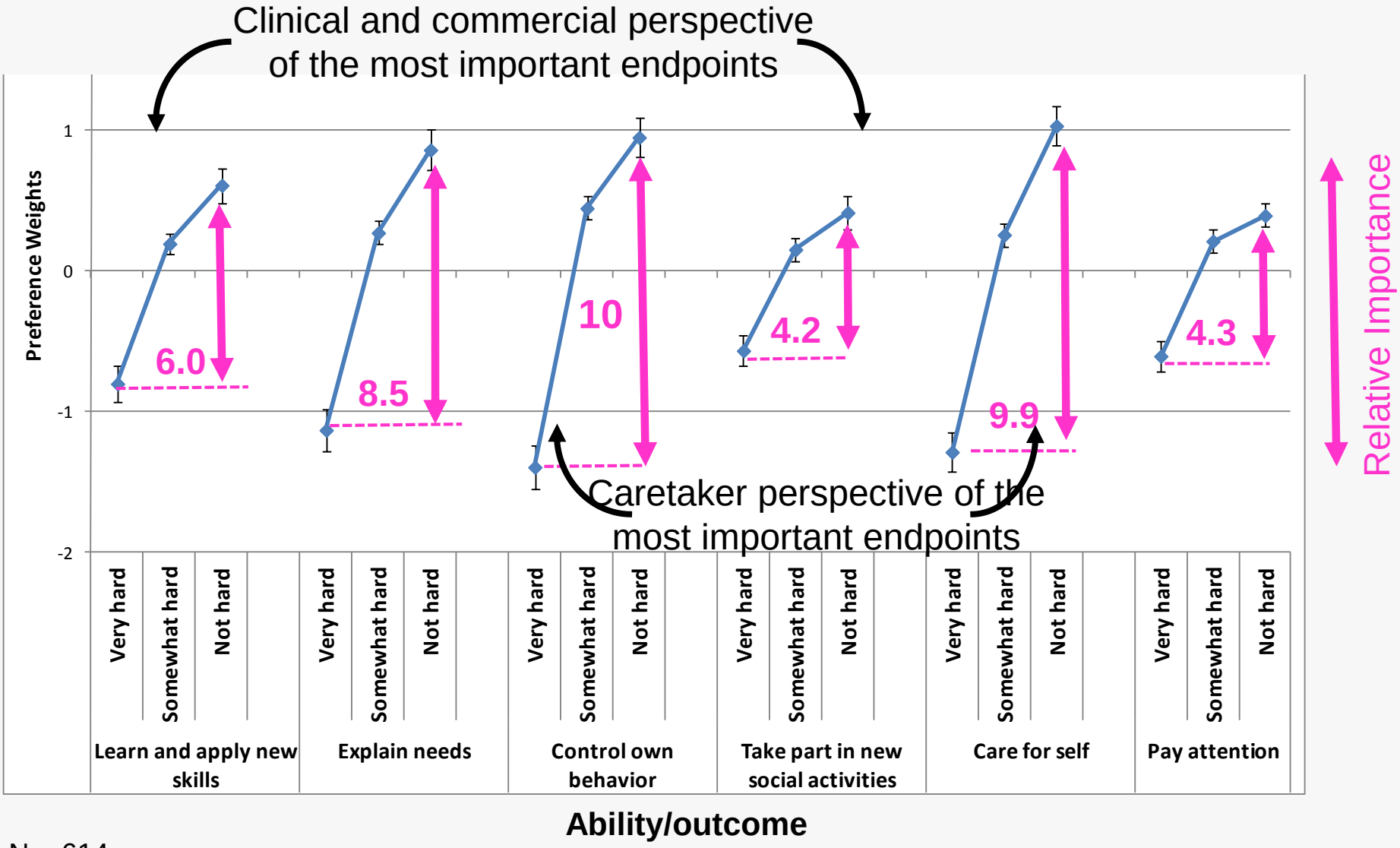


Levitan, Phillips, Walker, TIRS, **34** 564 – 573, (2014)

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

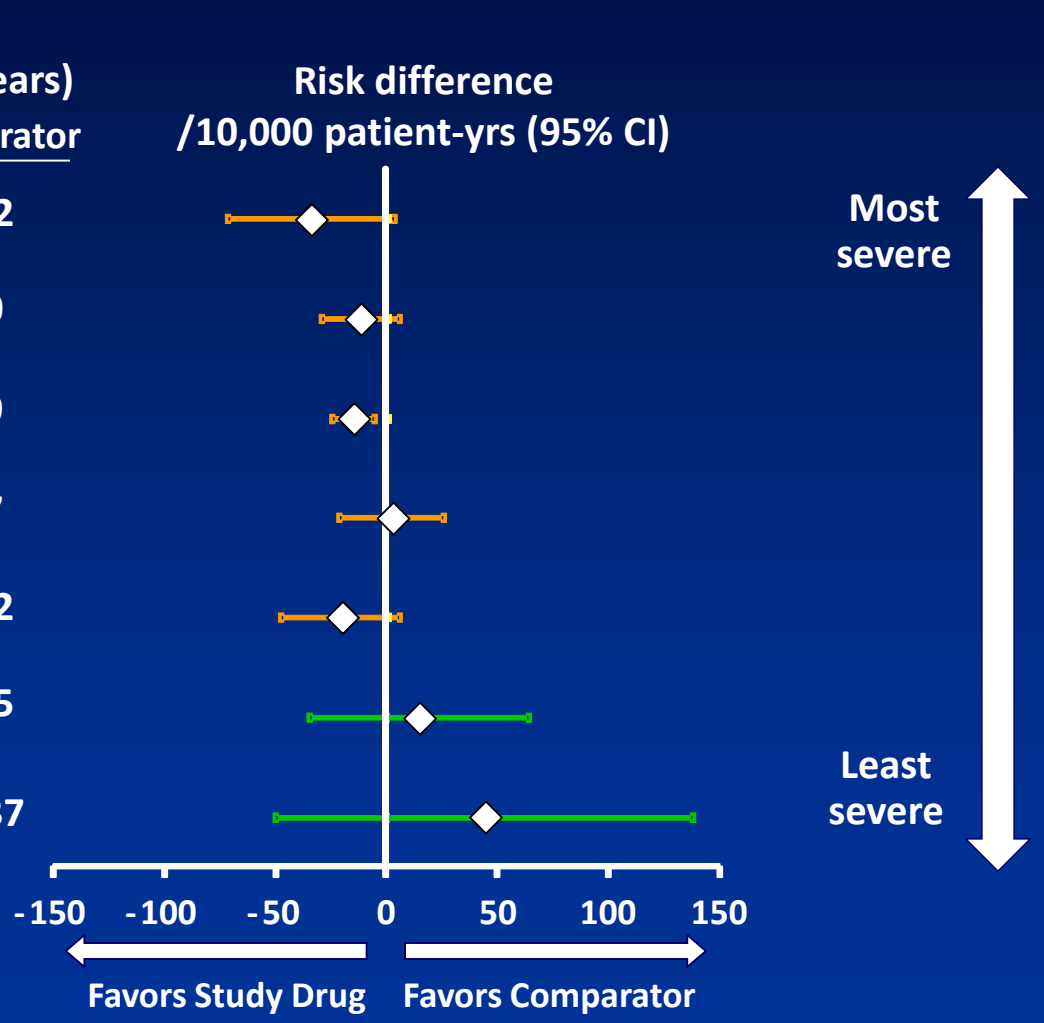


N = 614

J. Cross, CNS Summit, Nov, 2012

Risk Differences by Clinical Severity/Impact†
Atrial Fibrillation Example

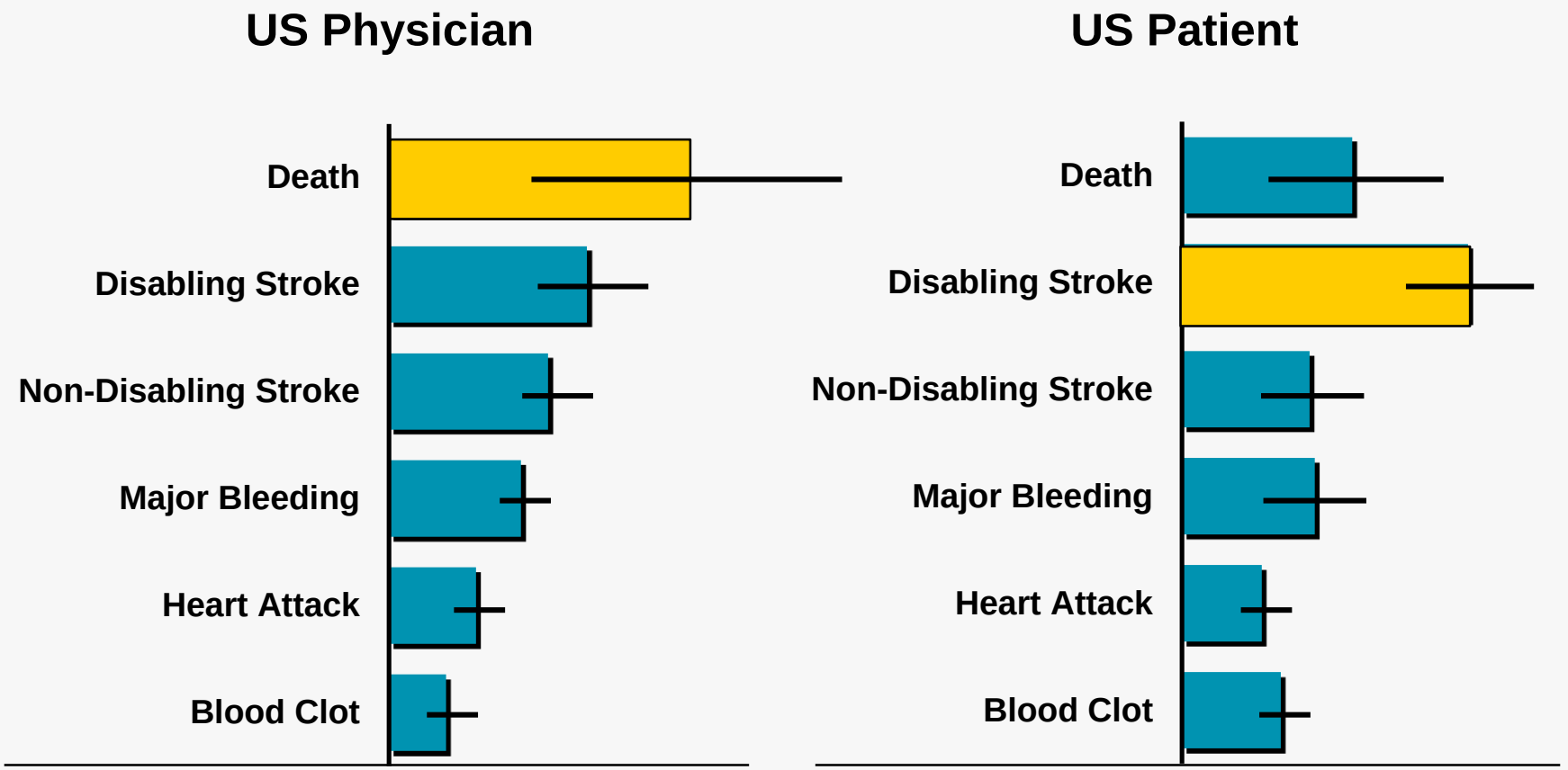
Endpoint	# of Events (/10,000 patient-years) Study Drug	Comparator
All-cause mortality	188	222
Disabling stroke	38	50
Non-CNS systemic embolism	4	19
Non-disabling stroke	79	77
Myocardial infarction	91	112
Major bleeding	360	345
Non-major clinically-relevant bleeding	1180	1137



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

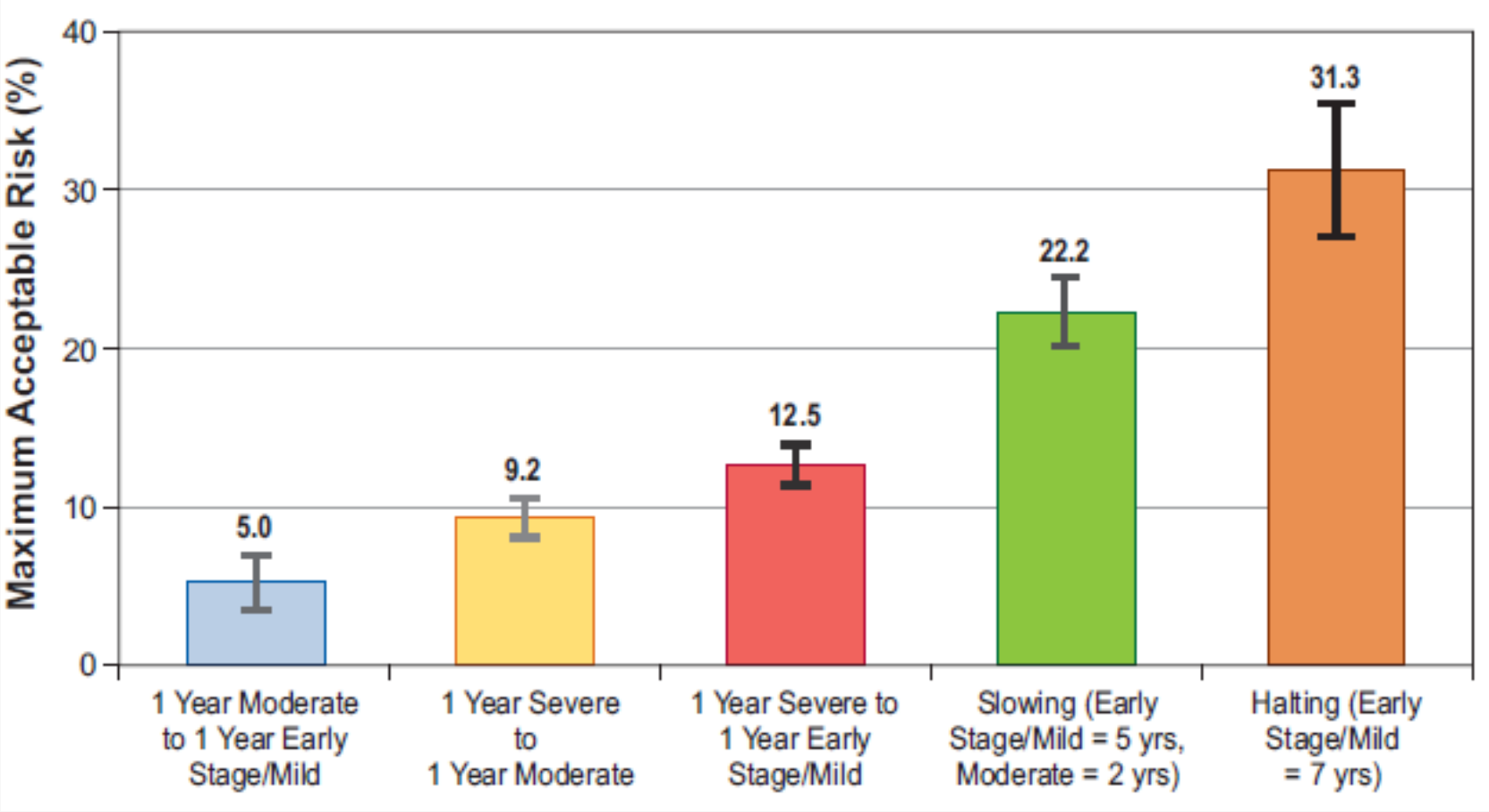
Identifying Differences Between Key Stakeholders

Preferences for Anticoagulants in Atrial Fibrillation



Levitan, Yuan, González, et al., ISPOR 18th Ann Int Mtg, 2013

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
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)