Patient-Centered Benefit-Risk Assessment (PCBR)

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MDIC Annual Meeting

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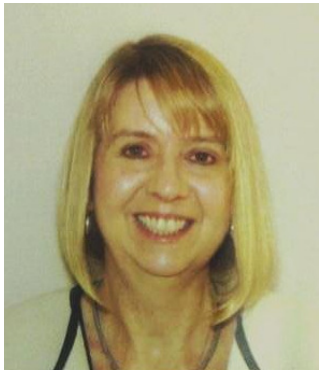
Speakers

Bennett Levitan, PhD

- Johnson & Johnson
- Director, Quantitative Safety Research, Department of Epidemiology, Janssen R&D of Johnson & Johnson

- Brett Hauber, PhD
  - RTI Health Solutions
  - Senior Economist, Vice President of Health Preference Assessment



- Diana Salditt
  - Medtronic
  - Distinguished Regulatory Affairs Advisor in Global Regulatory Affairs

Agenda

Project Overview: Patient-Centered Benefit-Risk Assessment in Medical Devices	Bennett Levitan
Methodology Catalog	Brett Hauber
Framework for Patient-Centered Benefit-Risk Assessments	Diana Salditt
Questions and Discussion	Bennett Levitan Brett Hauber Diana Salditt Telba Irony Stephanie Christopher

Project Overview: Patient-Centered Benefit-Risk Assessment in Medical Devices

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Project Overview

Vision

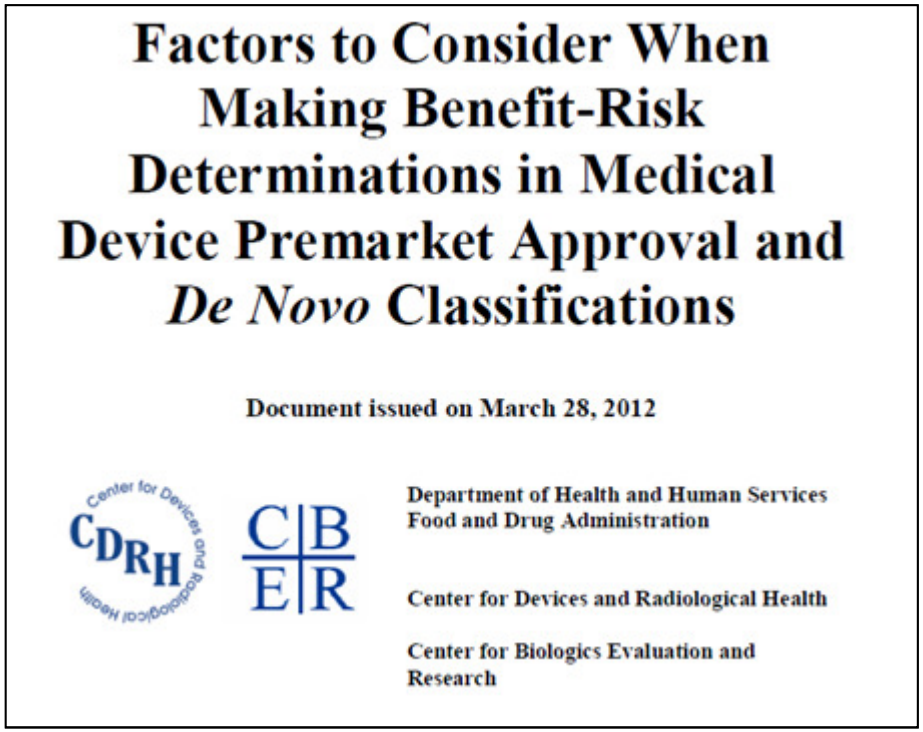
To establish a credible framework for defining patient preference regarding probable benefits and probable risks of a proposed medical device across a representative spectrum of conditions and patients who might be exposed to the device and the application of this information to premarket regulatory submissions and decisions.

Definition of Preferences

Qualitative or quantitative assessments of the relative desirability or acceptability of features that differ among alternative diagnostic or therapeutic strategies

Patient-Centered Benefit-Risk Assessment in Medical Devices

- FDA CDRH 2012 guidance on factors to consider for B-R assessment in devices
- Landmark policy statement:
  - First regulatory guidance on B-R worldwide
  - Still the only regulatory guidance for B-R in development worldwide



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

Key Elements of CDRH B-R Guidance

- Clear statement on the need for flexibility in B-R assessment
- Reflection on FDA's perspective on the role and interaction of critical components in applications, including severity of the condition, medical need, uncertainty, novelty, risk tolerance, risk mitigation, post-market data …
- Clear recognition of implications of learning for novel devices

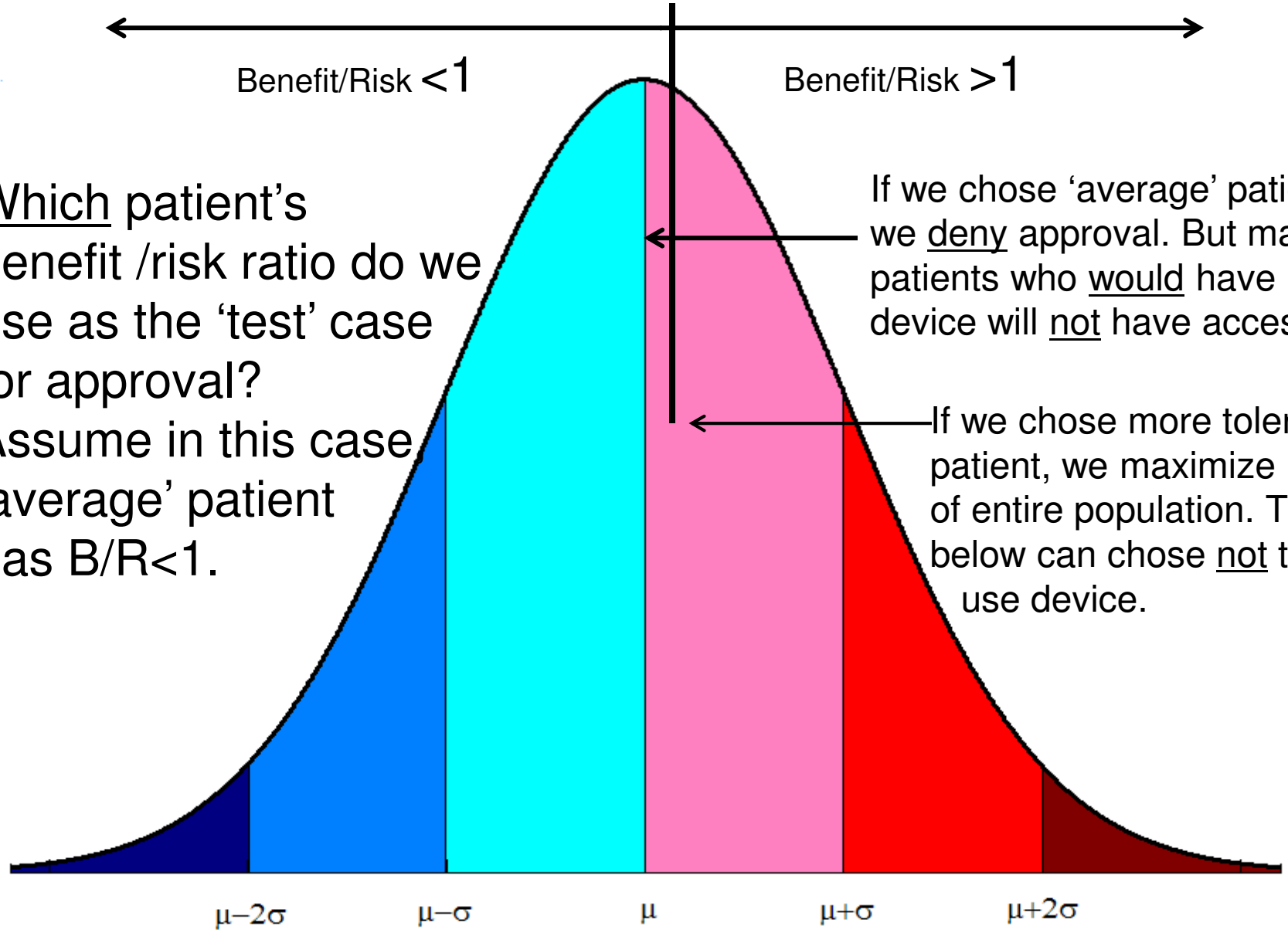
- Use and role of a patient-centered perspective

Patient-Centered B-R Assessment

- Guidance recognizes that risk tolerance will vary among patients. For example, tolerance for pain:
  - "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."
- Different patients may value benefits differently. Two obese patients may value the same amount of weight loss completely differently.
  - "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 requires that FDA review team puts itself into the shoes of potential patients to understand how patients will value benefits and risks of a device

Thanks to Jack W. Lasersohn



Distribution of Benefit Risk Value among patients for a Therapy

Thanks to Jack W. Lasersohn

Implications?

- Benefit-risk assessment is currently a key component for regulatory review, but it traditionally has been based on the regulatory/physician perspective
- CDRH B-R guidance suggests a much more critical role for the patient perspective
  - ➔ Some regulatory reviews may require a formal understanding of the patient view on B-R
- Treatments are currently approved based on efficacy and safety for subgroups defined by demographic or medical properties
  - ➔ Potential future where approval may include subgroups based on patient view of B-R

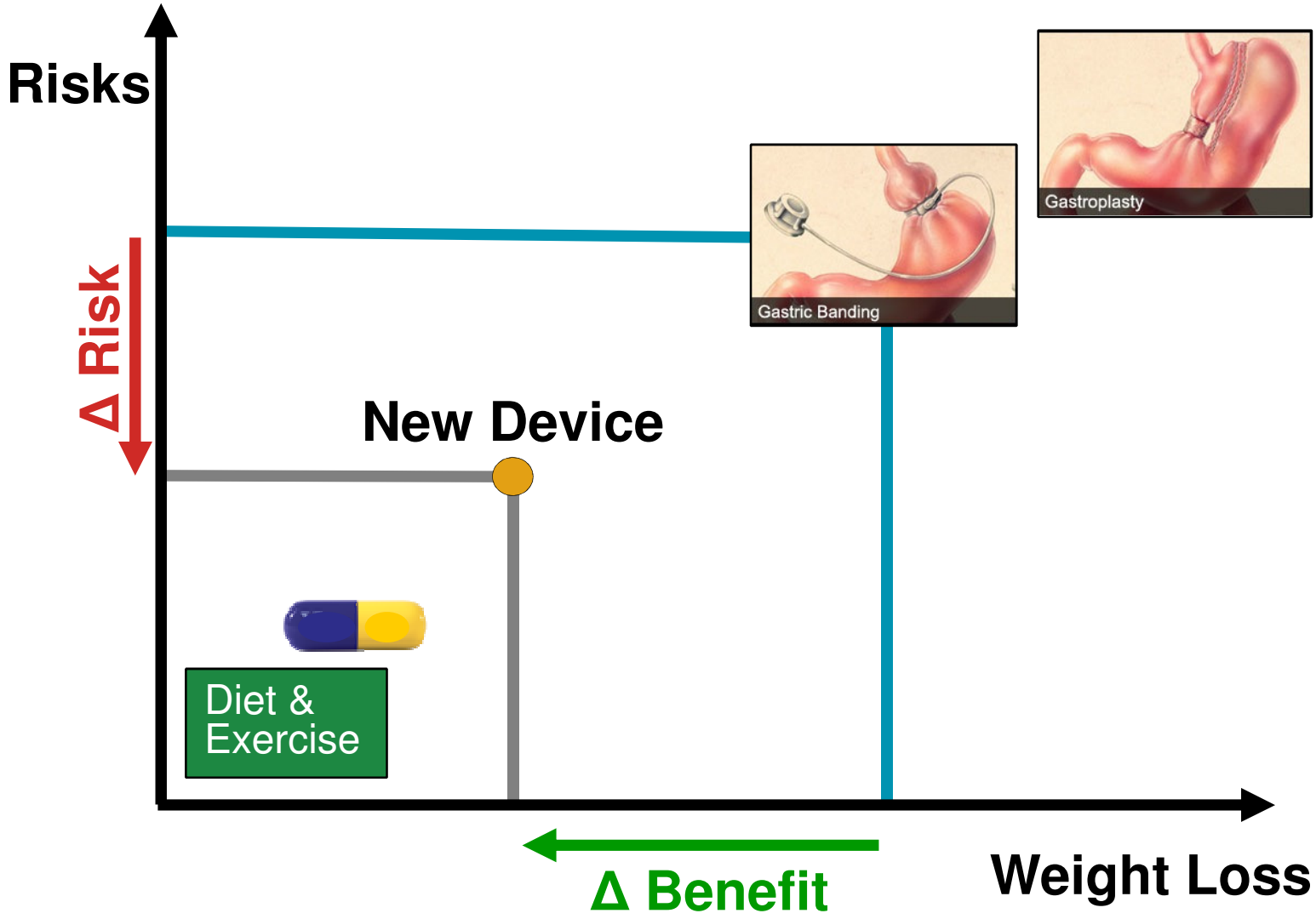
Many Roles for The Patient Perspective in Development

- Defining medical context
  - Nature of illness
  - Medical need
- Prototyping
- Study design
  - Designing recruitment
  - Endpoint selection
  - Peer advocate during informed consent
  - Reduce trial burden and time → reduced dropout
- Preference studies for benefit-risk
- Report results to patient community
- …

Lots of press, but not the whole story

Thanks to Bray Patrick-Lake (Duke) and CTTI

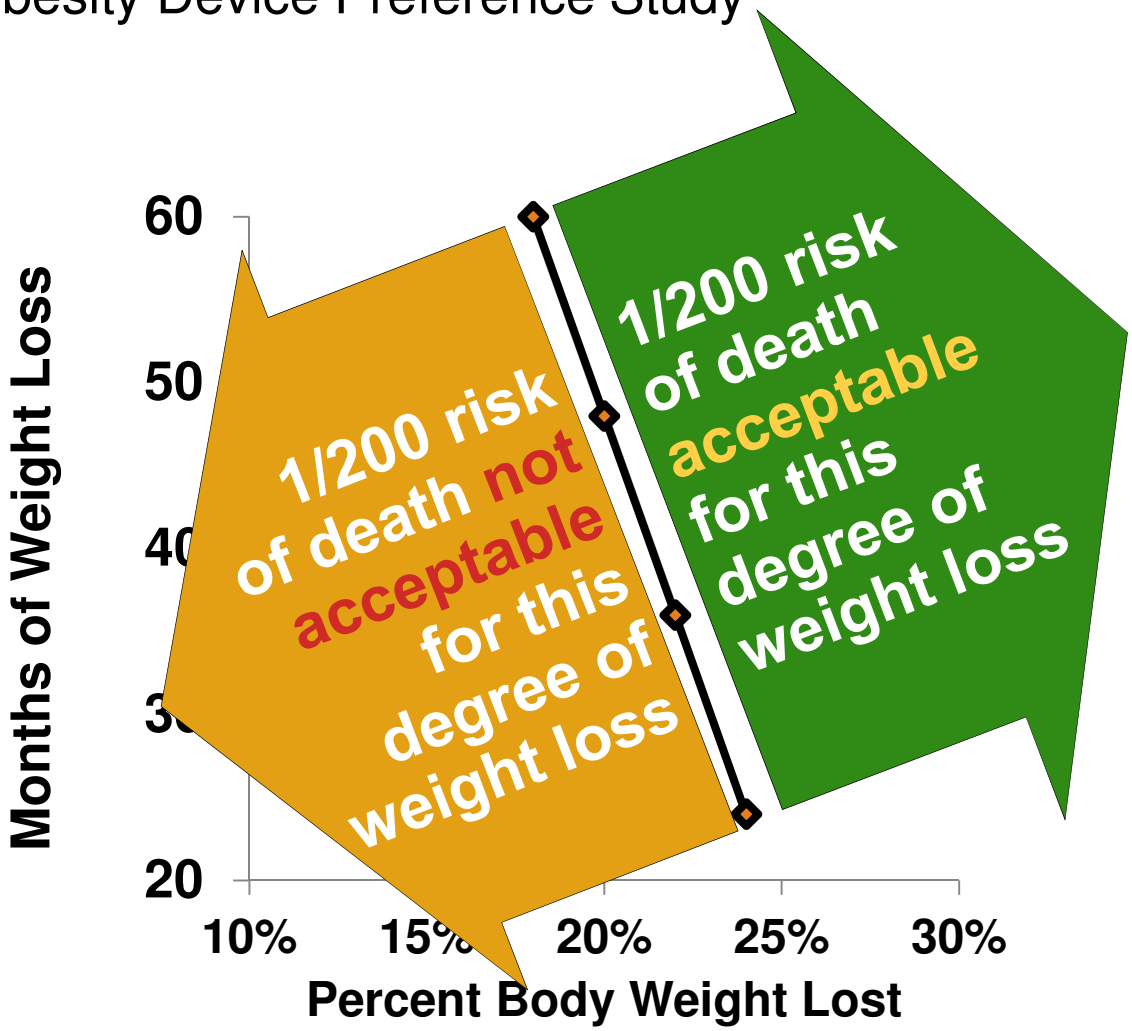
FDA CDRH Obesity Device Preference Study



CDRH / RTI project

Determining Detailed Thresholds for Maximum Acceptable Risk

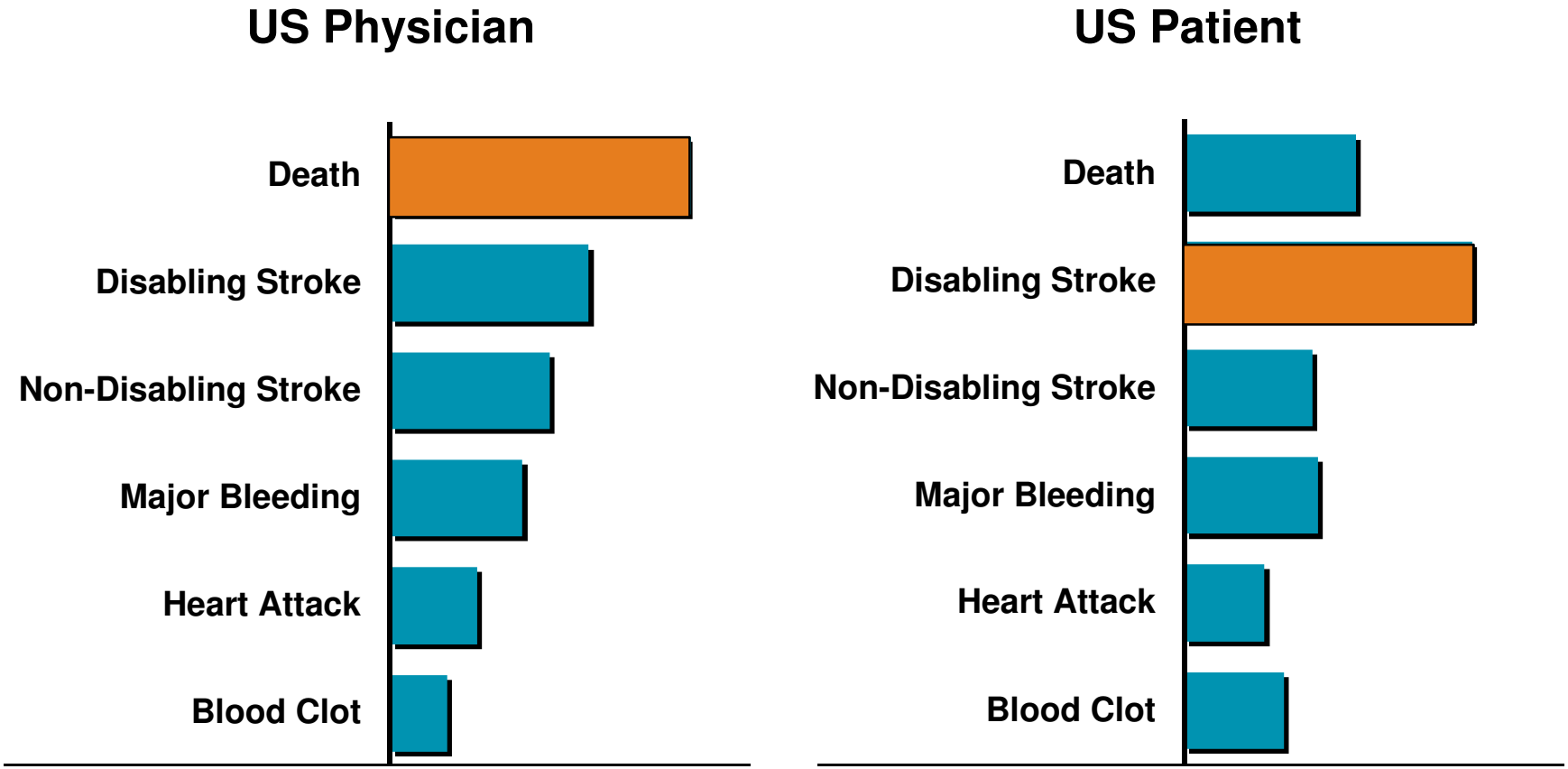
FDA CDRH Obesity Device Preference Study



CDRH / RTI project

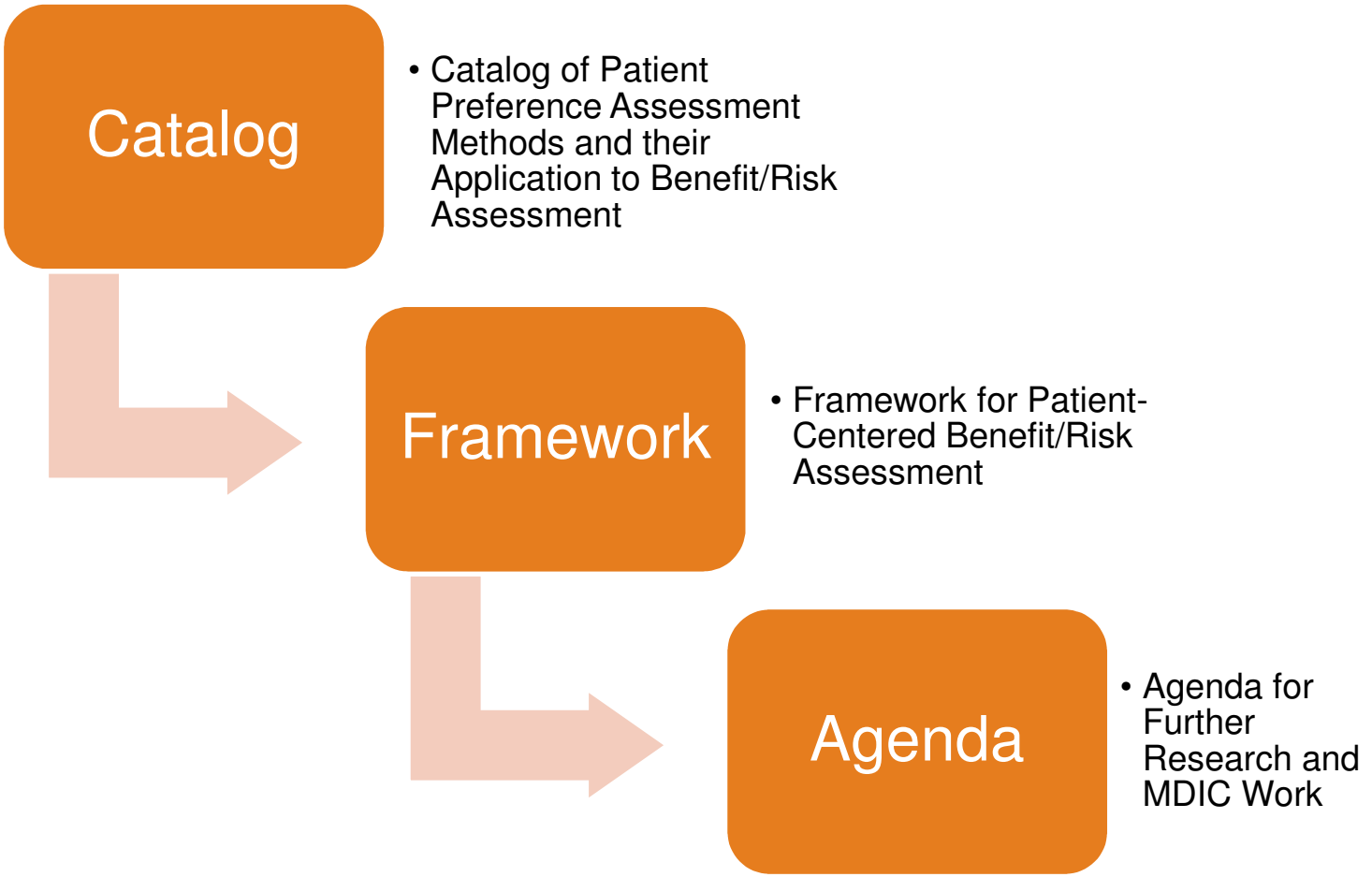
Identifying Differences Between Key Stakeholders

Preferences for Anticoagulants in Atrial Fibrillation



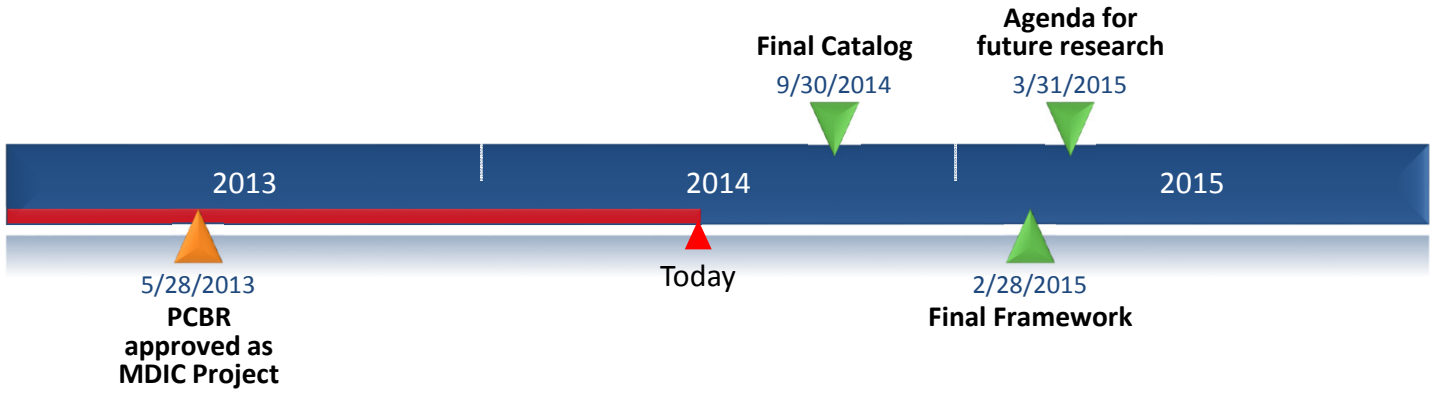
Levitan, Yuan, González, et al., ISPOR 18th Ann Int Mtg, 2013

PCBR Key Deliverables

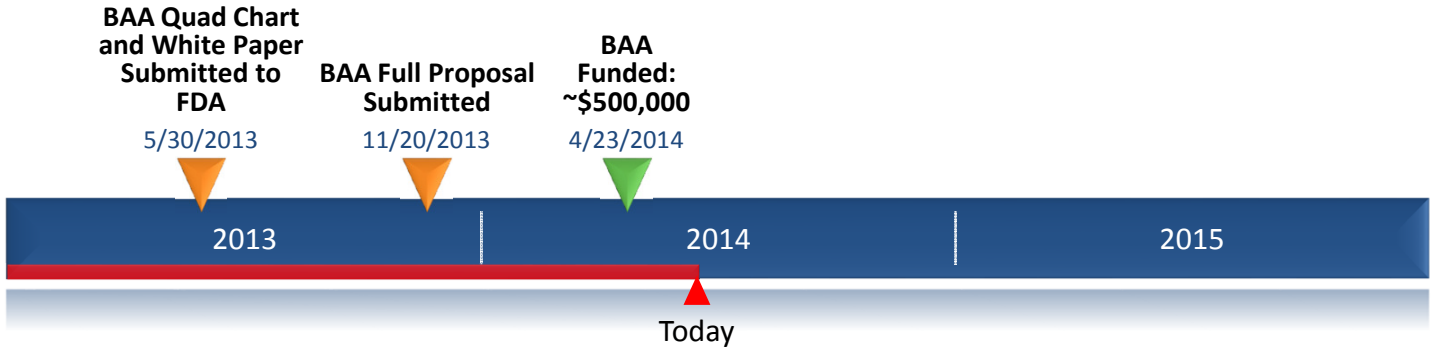


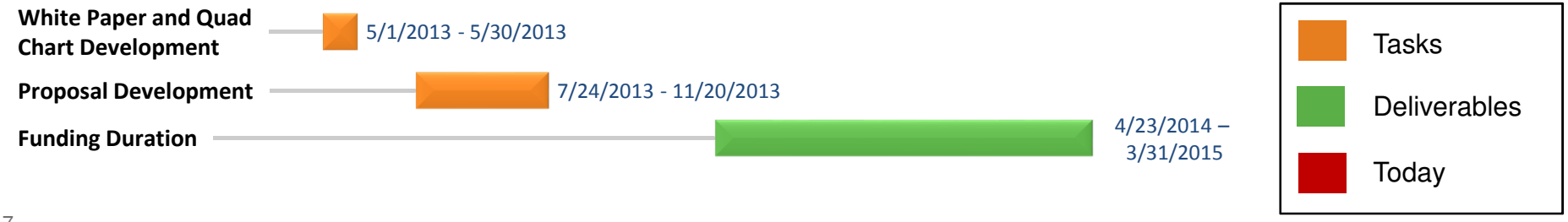
PCBR Project Timeline

Overview



Project Funding





Steering Committee Members

- Robert Becker, MD, PhD, CDRH/OIR, FDA
- Randall Brockman, MD, CDRH/ODE, FDA
- Jim Gardner, MD, MBA, Cook Group, Inc.
- Andrew Greenfield, AbioMed
- Arieh Halpern, Simulia
- Martin Ho, MSc, CDRH/Biostatistics, FDA
- Telba Irony, PhD, CDRH/Biostatistics, FDA
- Ross Jaffe, MD, NVCA, Versant Ventures; Board Champion, PCBR Project
- Richard Kuntz, MD, MSc, Medtronic
- Jack Lasersohn, JD, NVCA, The Vertical Group
- Bennett Levitan, MD, PhD, Janssen R&D, J&J
- Barry Liden, JD, Edwards Lifesciences
- Bryan Luce, MD, PhD, PCORI
- Kim McCleary, FasterCures
- Bryan Olin, PhD, Cyberonics
- Diana Salditt, Medtronic
- Peter Saltonstall, National Organization for Rare Disorders (NORD)

Committee Advisors

- Marc Boutin, JD, National Health Council
- Scott Braithwaite, MD, NYU School of Medicine
- Brett Hauber, PhD, RTI International
- Bray Patrick-Lake, MFS, Clinical Trials Transformation Initiative (CTTI)
- Kelly Slone, NVCA, Interim Project Manager for PCBR initiative
- Sean Tunis, MD, MSc, Center for Medical Technology Policy

Preference Methodology Catalog

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Preference Methodology Catalog

Objectives

- Assess the methods that are currently available to quantify patients' benefit-risk preferences
- Evaluate the applicability of available methods to benefit-risk assessments at different stages in the product lifecycle
- Identify gaps in the availability of methods or the ability of existing methods to support benefit-risk assessment

Project Overview

- Phase 1: Develop a Preference-Methodology Catalog
- Phase 2: Evaluate Methods Across the Product Lifecycle
- Phase 3: Conduct a Gap Analysis

Criteria for Methods included in Catalog

- Provides information on relative importance of or tradeoffs among features that differ among alternative health interventions or diagnostic strategies, either directly or indirectly
- Methodology, analysis, and proper interpretation published in peer-reviewed literature
- Application of methods to health interventions
- Not restricted to either quantitative or qualitative methods
- Not restricted to a particular type of stakeholder

Evaluation of Methods: Methodology and Sample

- Methodology
  - How data are obtained (simple structured interview, direct elicitation, indirect elicitation, decision aids)
  - Reliance on hypothetical scenarios
  - How detailed a description of the attributes can realistically be given to patients with the method?
  - How well can the appropriateness of the method for a given type of problem be assessed in advance?
- Sample
  - Sample size requirements
  - Time needed by patients
  - Disease knowledge needed by patients
  - Potential use of surrogates (ex: for young patients, dementia, etc.)

Evaluation of Methods: Analysis and Validation

- Analysis
  - Statistical rigor
  - Impact of uncertainty in benefits/harms on the method and its analysis
  - Ability to detect heterogeneity in preferences
  - Ability to detect preference heterogeneity over time
  - Ability to detect risk tolerance
  - Ease of communication/interpretation of results
  - Generalizability of results
- Validation
  - What types of validation tests are appropriate?
  - Validation measures that have been applied to each method
  - Validation measures that could be applied to each method

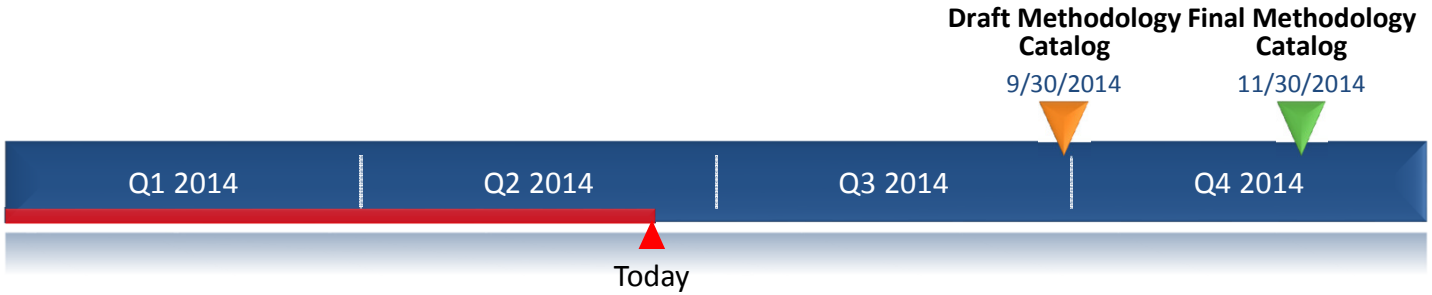
Evaluation of Methods: Resources and Prior Use

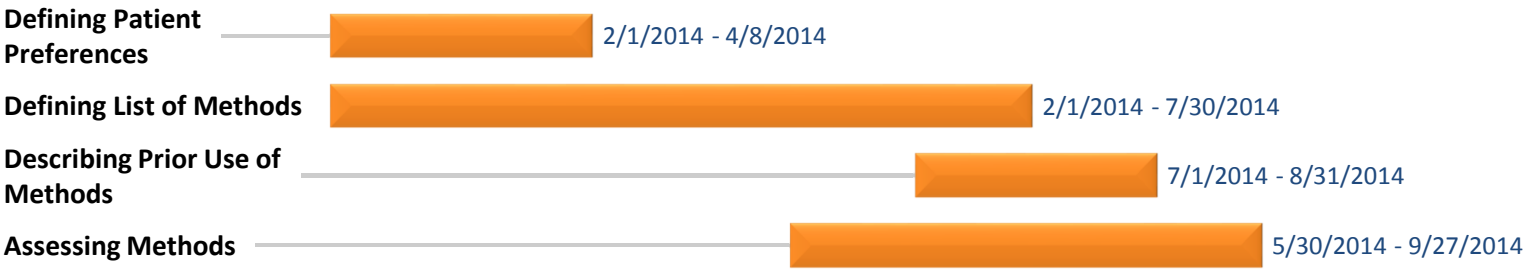
- Resources required for implementation
  - Software requirements
  - Time to implement
  - Cost to implement
- Relevant examples of prior use
  - What were the main research questions?
  - What were the key results from those questions?
  - How were the results applied?

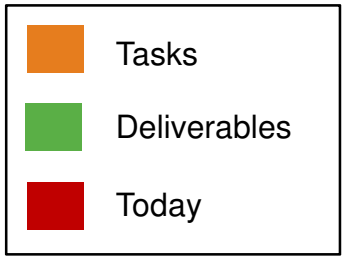
Methods to Include

- Qualitative
  - Structured interviews or discussions
  - Ranking exercises
  - Sentiment analysis (web trolling)
- Structured weighting
  - Swing weighting
  - Point allocation or “100 coins” approaches
  - Analytical hierarchy process, MACBETH, and variants
- Health state utility
  - Standard gamble
  - Time tradeoff
- Stated preference surveys
  - Rating questions
  - Direct assessment questions
  - Stated behavior
  - Threshold techniques
  - Conjoint analysis / discrete choice experiments
  - Best-worst scaling
- Revealed preference
  - Patient preference trials
  - Direct questions in clinical trials
  - “Norton method”
  - Informed consent

PCBR Project Timeline: Catalog







Catalog Working Group

- RTI Health Solutions
  - Principal Investigator
    - Brett Hauber, PhD, Senior Economist, Health Preference Assessment
  - Other RTI Staff
    - Juan Marcos González, PhD, Technical Contributor
    - Margaret Mathes, Medical Editor
    - Kimberly Moon, Project Manager

- Academic experts and consultants
  - Scott Braithwaite, NYU School of Medicine
  - Ken Deal, McMaster University
  - James Dolan, University of Rochester
  - Bennett Levitan, Janssen R&D J&J
  - Bryan Luce, PCORI
  - Bray Patrick-Lake, Clinical Trials Transformation Initiative

Framework for Patient-Centered Benefit-Risk Assessment

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Framework Documents

- Framework requirements
- Framework report

Framework Requirements

- Document that establishes the requirements and describes the limitations of the framework
- Content
  - Purpose
  - Applicability
  - Balance
  - Transparency
  - Usefulness
  - Living Document
  - Limitations

Framework Report

- Framework Report: overarching report of PCBR Project
  - Resource for CDRH, MDIC members, and industry on when and how to collect patient preference information for incorporation into regulatory process
  - Would incorporate Catalog Report and Gap Analysis
- Proposed deliverable dates:
  - Initial draft of Framework: September 2014
  - Revision and incorporation of draft Catalog: Nov 2014
  - Finalization with Catalog and Gap Analysis: March 2015

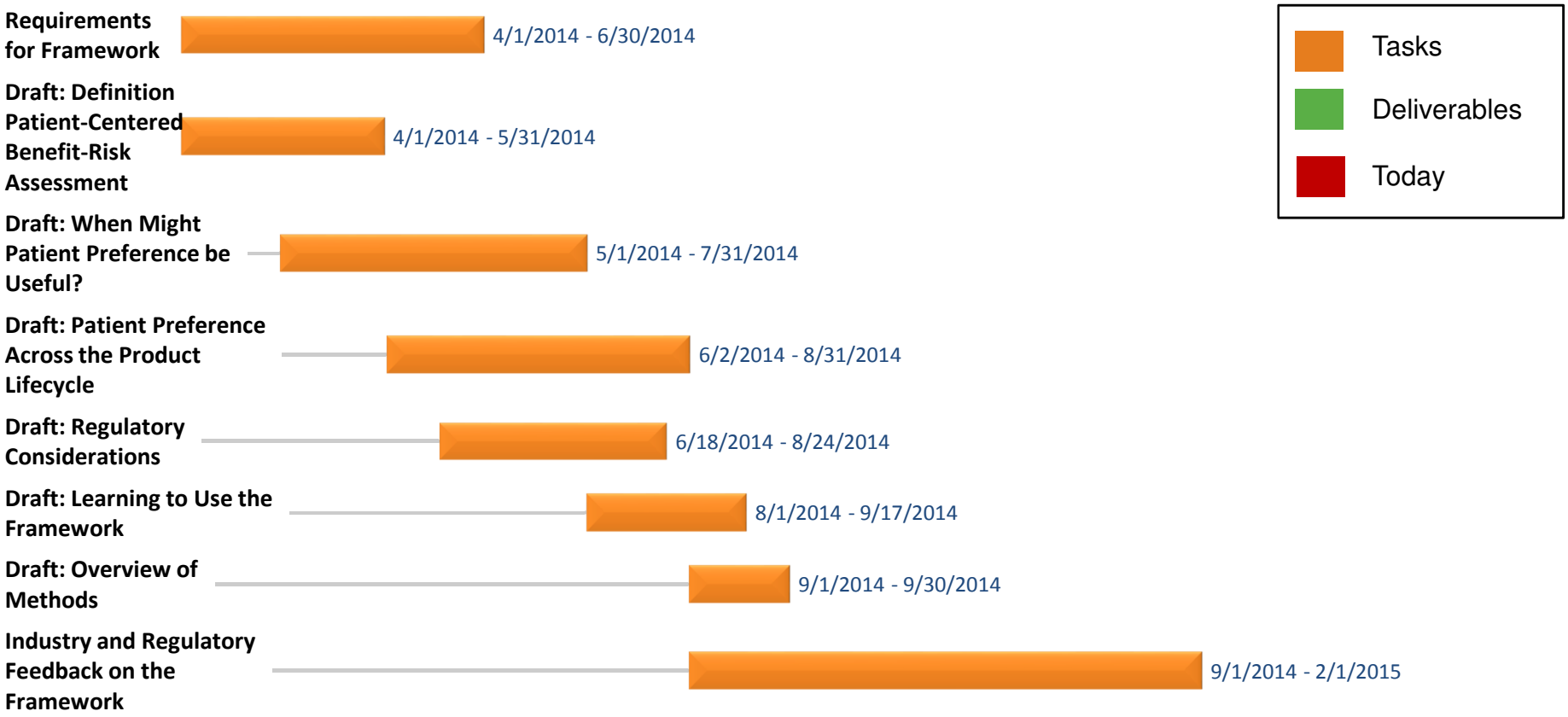
Framework Report Outline

- Introduction
- Definition of Patient-Centered Benefit Risk Assessment and Background Concepts
- For What Medical Device Applications is Patient Preference Info Potentially Valuable in the Regulatory Process?
- Patient Preference Needs in the Regulatory Product Lifecycle
- Overview of Methods for Assessing Patient Preferences
- Regulatory Considerations in using Patient Preference Information
- Value of Patient Preference Information Developed for Regulatory Purposes to Others in the Health Care System
- Opportunities for CDRH and Industry to Learn How to Use Patient-centered Benefit Risk Assessment in the Regulatory Process

Key Challenges

- Developing an Approach to Assessing the Value of Patient Preference Information for Specific Situations
- Recognizing and Reconciling the Perspectives of Multiple Stakeholders
- Characterizing the Value of Preference Information Over Time – Regulatory Novelty and Product Lifecycle Considerations
- Maximizing the Utility of Patient Preference Information

PCBR Project Timeline: Framework



Framework Working Group

- Ross Jaffe, Versant Ventures
- Randy Brockman, FDA
- Telba Irony, FDA
- Bennett Levitan, Janssen R&D
- Barry Liden, Edwards Lifesciences
- Carolyn Neuland, FDA
- Frank Hurst, FDA
- Bryan Olin, Cyberonics
- Bray Patrick-Lake, Clinical Trials Transformation Initiative
- Diana Salditt, Medtronic
- Sean Tunis, Center for Medical Technology Policy

Questions and Discussion

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Definition of Preferences: Criteria

- Can capture perspectives of patients
- Allows for characterizing preferences for desirable outcomes or effects and acceptability of undesirable outcomes or effects
- Includes the relative nature of preferences (i.e., allows for direct or indirect comparison across features)
- Allows for qualitative and quantitative characterization of preferences
- Applicable to all diagnostic or therapeutic strategies