



CALIFORNIA TECHNOLOGY
ASSESSMENT FORUMSM

**CardioMEMSTM HF System and
Sacubitril/Valsartan (EntrestoTM) for
Management of Congestive Heart Failure**

Public Meeting

October 29, 2015

CTAF Overview

- Core program of the Institute for Clinical and Economic Review (ICER)
- Goal: Help patients, clinicians, insurers, and policymakers understand and apply evidence to improve the quality and value of health care
- Deliberation and voting by CTAF Panel – independent clinicians, methodologists, and public representatives
- Supported by grants from the Blue Shield of California Foundation, the California HealthCare Foundation, and the Laura and John Arnold Foundation

Agenda

- **Public Meeting Convened, Topic Overview** | 10:00 am
- **Presentation of the Evidence and Economic Modeling, Q&A** | 10:05 – 11:20 am (Dr. Dan Ollendorf, Dr. Alex Sandhu)
- **Public Comments** | 11:20 am – 12:00 pm
- **Lunch** | 12:00 – 12:45 pm
- **CTAF Q&A with Clinical Experts / Deliberation and Votes** | 12:45 – 1:30 pm
- **Break** | 1:30 – 1:45 pm
- **Policy Roundtable Discussion, Best Practice/Policy Recommendations** | 1:45 – 3:25 pm
- **Reflections from CTAF Panel** | 3:25 – 3:40 pm
- **Summary and Closing Remarks** | 3:40 – 3:45 pm
- **Meeting Adjourned** | 3:45 pm
 - **Download meeting materials:** <http://tinyurl.com/CTAF-CHF>



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Evidence Review

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October 29, 2015

Disclosures:

I have no conflicts of interest.

Key review team members:

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Topic in Context

- (Congestive) heart failure (CHF): Fluid build-up as the heart muscle inefficiently fills with or pumps out blood
- Affects over 6 million individuals in US
- High degree of morbidity:
 - Measured using limitations on physical activity from symptoms (NYHA classes I – IV)
 - 5-year mortality similar to many cancers (40-50%)
 - High rates of hospitalization and intensive outpatient care

Recent Interventions for CHF

- **CardioMEMS™ HF System (St. Jude Medical, Inc.)**
 - Wireless sensor implanted in pulmonary artery (PA): Elevated PA pressure correlated with worsening CHF
 - Pressure readings transmitted to secure online database where physicians can track pressure data and make necessary adjustments to therapy
 - FDA-approved May 2014
- **Sacubitril/Valsartan (Entresto™, Novartis AG)**
 - Combination of neprilysin inhibitor (sacubitril) to maintain fluid balance and angiotensin II receptor blocker (valsartan) for lowering of blood pressure and improved hemodynamics
 - FDA-approved July 2015

Methods

- Separate evaluations of the comparative clinical effectiveness and comparative value of CardioMEMS and Entresto
- Based primarily on Phase II/III RCTs
- *Target populations (FDA indications):*
 - CardioMEMS: Adults with NYHA Class III CHF who have been hospitalized in prior 12 months
 - Entresto: Adults with NYHA Class II-IV CHF and reduced ejection fraction (<35-40%)

Methods (2)

- *Comparators:*
 - CardioMEMS: typical management based on patient signs and symptoms
 - Entresto: angiotensin-converting enzyme (ACE) inhibitor therapy
- *Outcomes:*
 - Mortality
 - Hospitalization and emergency department (ED) visits
 - Quality-of-life (QoL) and CHF symptoms
 - Complications and drug-related adverse effects

CARDIOMEMS

Clinical Evidence

- CHAMPION Trial:
 - Single-blind RCT (n=550) of CardioMEMS w/ vs. w/o transmission of PA pressure data in Class III patients / CHF-related hospitalization in prior 12 months
 - Daily PA pressure readings sent to clinicians
 - Single-blind follow-up for 6 months; blind broken thereafter for additional follow-up (mean overall f/u: 15 months)
 - Study powered to detect differences in number of CHF-related hospitalizations at 6 months

CHAMPION: Effectiveness

- CHF Hospitalization:
 - 6 months: 84 hospitalizations for CardioMEMS vs. 120 for controls (HR: 0.72; 95% CI: 0.60, 0.85; $p=0.0002$). NNT: 8
 - 15 months: 158 vs. 254 for controls (HR: 0.63; 95% CI: 0.52, 0.77; $p<0.0001$). NNT: 4
 - Mean length of stay in hospital: 2.2 vs. 3.8 days ($p=0.02$)

CHAMPION: Effectiveness (2)

- Mortality:
 - Only assessed as part of composite supplementary endpoint
 - 15-months: 107 patients died or hospitalized vs. 138 for controls (HR: 0.73; 95% CI: 0.57, 0.94; $p=0.0146$)
- Quality of life:
 - Statistically-significant but modest improvement at 6 months (-10.6 vs. -7.4, $p=0.04$)

CHAMPION: Harms

- No device- or system-related complications in 98.6% of patients
- 15 serious adverse events:
 - 8 related to device or system (1%), 7 related to implant procedure (1%)
 - Bleeding most common
 - Other:
 - Hospitalizations related to anticoagulation during implant
 - Pulmonary thrombus during right-heart catheterization
 - Cardiogenic shock

CHAMPION: Subgroup Analyses

- Reduction in rate of CHF hospitalization similar in patients with and without:
 - Pulmonary hypertension (at time of implantation)
 - Chronic obstructive pulmonary disease
- Lower hospitalization rates in both kinds of CHF (17.6 months follow-up)
 - Patients with preserved ejection fraction
 - HR 0.50; 95% CI: 0.35, 0.70; $p < 0.0001$
 - Patients with reduced ejection fraction
 - HR 0.74; 95% CI: 0.63, 0.89; $p < 0.001$

CHAMPION: Controversies and Uncertainties

- Communications from study nurses to treating physicians
- Subgroup data suggesting no benefit in women?
- No published separate analysis of mortality
- FDA approval required two post-marketing studies:
 - Device effectiveness in men vs. women
 - Real-world effectiveness in certain clinical subgroups

CardioMEMS: Summary

- Moderate certainty of small net benefit vs. usual monitoring of signs and symptoms
- Small (less than 10%) chance that net health benefit could be negative:
 - Further study may show equivalent clinical effectiveness, especially in real-world settings, and patients will always face small risk of serious harms with device placement
- ICER's overall evidence rating
 - Promising but inconclusive
- Other benefits or disadvantages: anxiety or reassurance from permanent device placement

ENTRESTO

Clinical Evidence

- PARADIGM-HF Trial:
 - Double-blind RCT (n=8,442) of Entresto vs. enalapril in Class II-IV patients with ejection fraction $\leq 35\%$
 - Mean age 64; 78% male
 - Stopped early (median of 27 months) because evidence of “overwhelming benefit” detected in interim analysis

PARADIGM-HF: Effectiveness

- Composite outcome measure of CV death or first CHF hospitalization:
 - 21.8% for Entresto vs. 26.5% for enalapril groups
 - HR 0.80; 95% CI: 0.73, 0.87; $p < 0.001$
- Similar results for most other key outcomes:

Event	NNT
Death from cardiovascular causes or first hospitalization for worsening CHF	21
Death from cardiovascular causes	31
First hospitalization for worsening CHF	36
Death from any cause	36
Emergency department visit	83

PARADIGM-HF: Effectiveness (2)

- Worsening of CHF:
 - Among those surviving at 12 months
 - 6.1% for Entresto vs. 7.4% for enalapril (p=0.023)
- Quality of life:
 - Less reduction over time in QoL with Entresto
 - -2.99 vs. -4.63 for enalapril, p=0.001

PARADIGM-HF: Harms

- Overall serious adverse event rates comparable between groups
- Discontinuation of study drug due to adverse events lower with Entresto
 - 10.7% vs. 12.3% for enalapril, $p=0.03$
- Incidence of angioedema nominally higher with Entresto
 - 0.5% vs. 0.2% for enalapril, but not statistically significant

PARADIGM-HF: Subgroup Analyses

- Effectiveness of Entresto similar across pre-specified subgroups (sex, age, race, medical/HF history, ejection fraction)
- Angioedema more common in black patients receiving Entresto (2.3% vs. 0.5% for enalapril)
 - FDA requiring post-marketing safety study

PARADIGM-HF: Controversies and Uncertainties

- Valsartan alone a more appropriate comparator?
 - Currently not possible to discern relative contributions of sacubitril and valsartan to outcome
- PARADIGM-HF limited to patients who tolerated a “run-in” phase (>11% did not)
- Theoretical correlation of chronic neprilysin inhibition with cognitive impairment
 - FDA requiring post-marketing RCT vs. valsartan alone

Entresto: Summary

- Moderate certainty of small to substantial net benefit vs. enalapril
- ICER's overall evidence rating:
 - Incremental or better
- No other benefits or disadvantages noted

Public Comments Received

- CardioMEMS
 - CHAMPION trial not powered to detect mortality differences and should not be penalized for this
 - FDA acknowledged limitations of additional analyses but found evidence of positive treatment effect
- Entresto
 - No comments on evidence review



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Comparative Value Analysis

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October 29, 2015

Disclosures:

I have no conflicts of interest.

Key review team members:

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Rick Chapman, PhD, MS

Dan Ollendorf, PhD

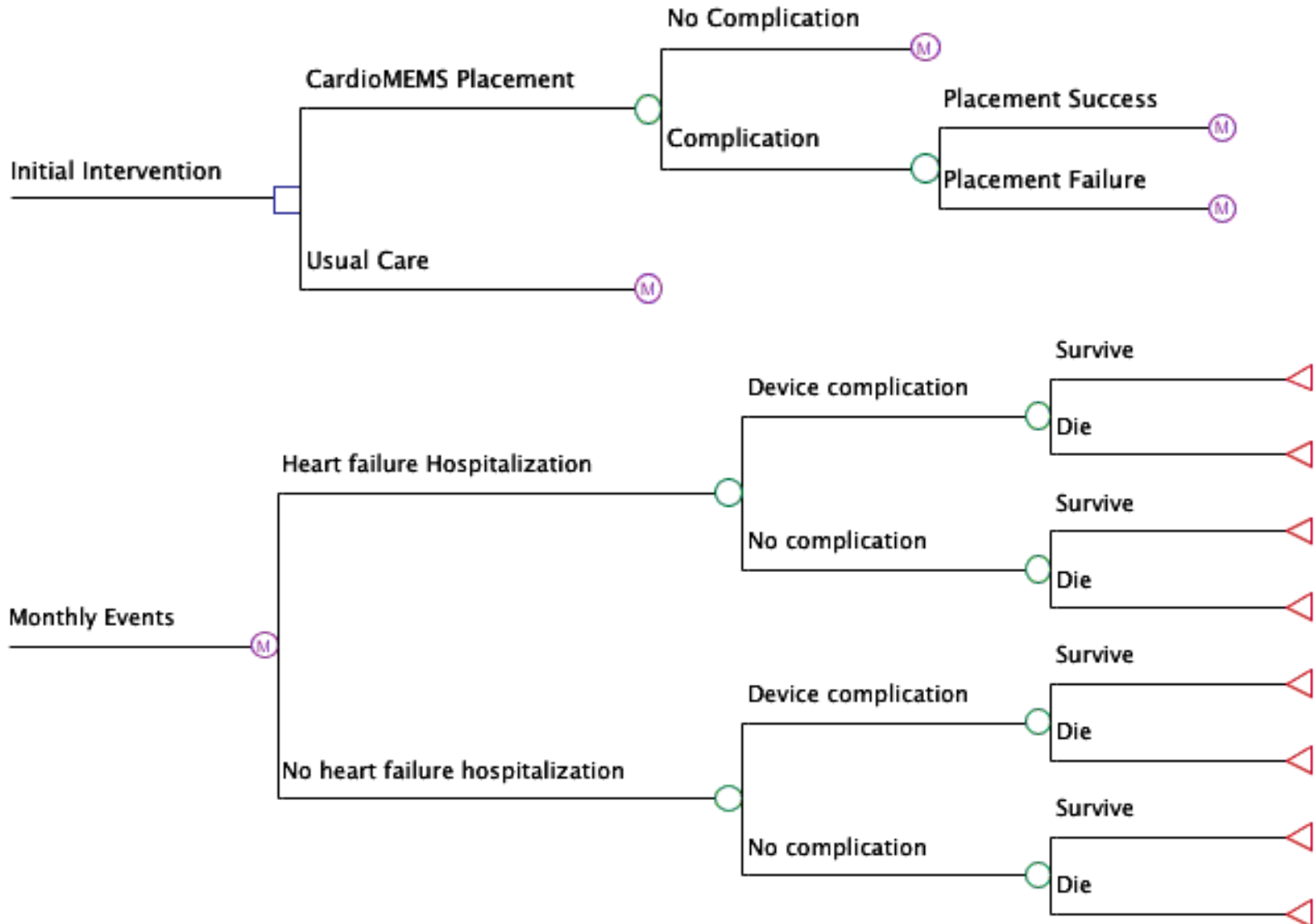
Research Questions

1. What are the outcomes, costs, and cost-effectiveness of the CardioMEMS HF monitoring system compared with usual care?
2. What are the outcomes, costs, and cost-effectiveness of Entresto compared with ACE-inhibitor therapy?

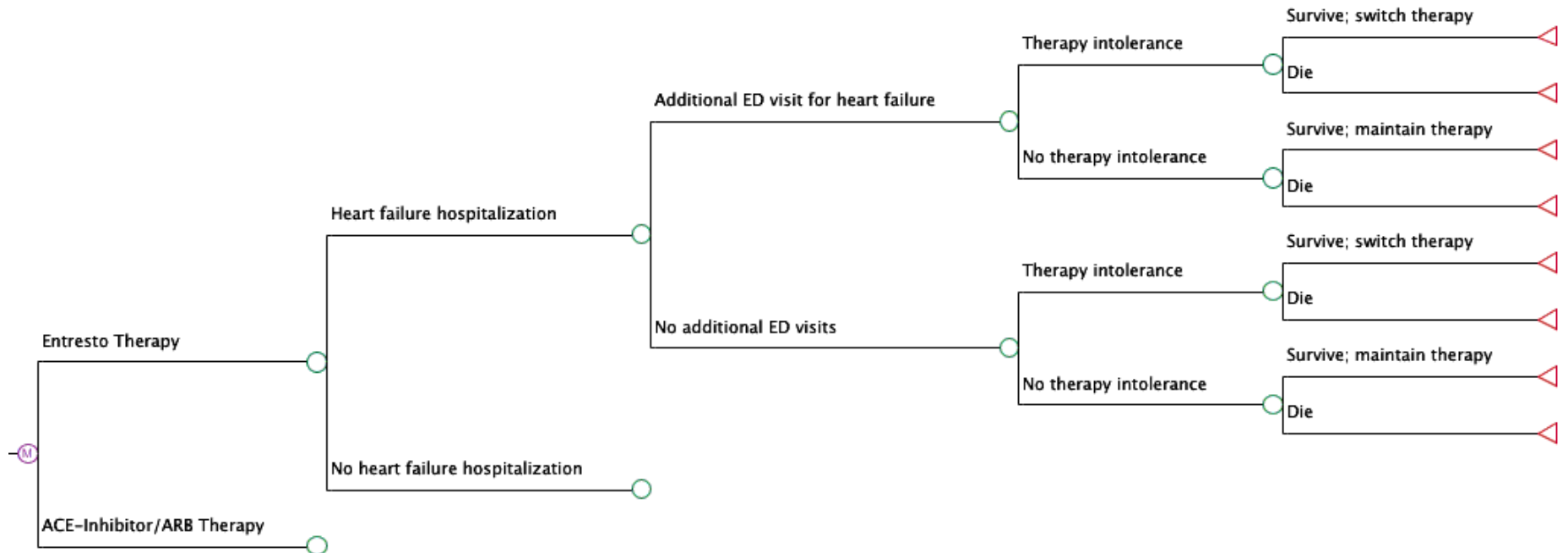
Methods

- Population
 - CardioMEMS: CHAMPION trial population
 - 62-year-old men and women with NYHA Class III heart failure
 - Reduced ejection fraction and preserved ejection fraction
 - Previous heart failure hospitalization within 12 months
 - Entresto: PARADIGM-HF trial population
 - 60-year-old men and women with NYHA Class II-IV heart failure
 - Reduced ejection fraction
- “Payer perspective”: direct medical care and drug/device costs
- Lifetime horizon

CardioMEMS Model Structure



Entresto Model Structure



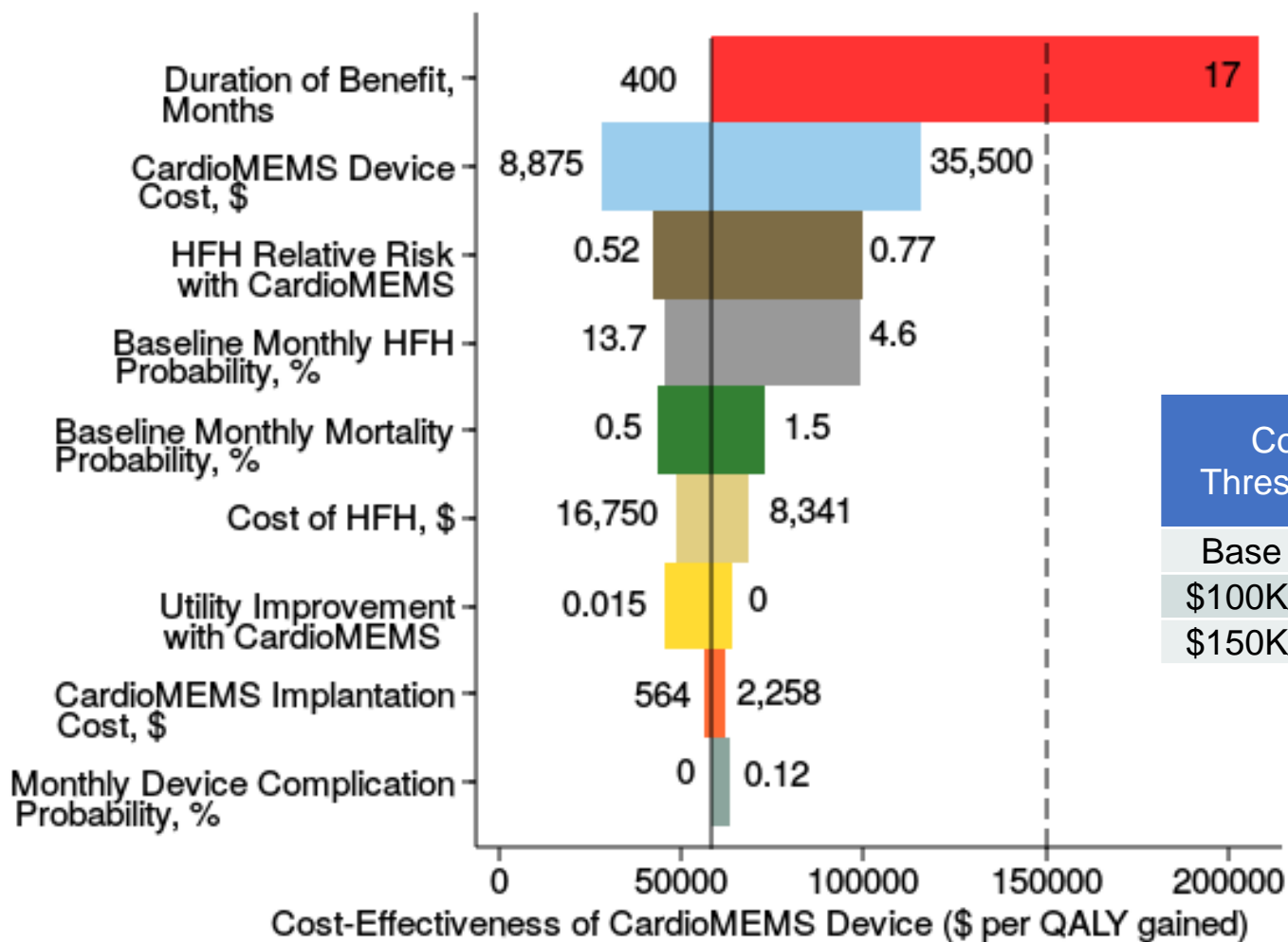
Results: CardioMEMS Base Case

CardioMEMS vs. Usual Care: Entire Cohort

Arm	Heart Failure Hospitalizations	Life-years	QALYs	Cost (\$)	Incremental Cost-Effectiveness Ratio (\$/QALY gained)
Usual Care	3.18	5.28	2.44	156,764	---
CardioMEMS	2.19	5.72	2.74	174,037	57,933

Results: CardioMEMS

One-way Sensitivity Analyses



Cost Thresholds	Monthly Monitoring Cost
Base Case	\$27
\$100K/QALY	\$209
\$150K/QALY	\$427

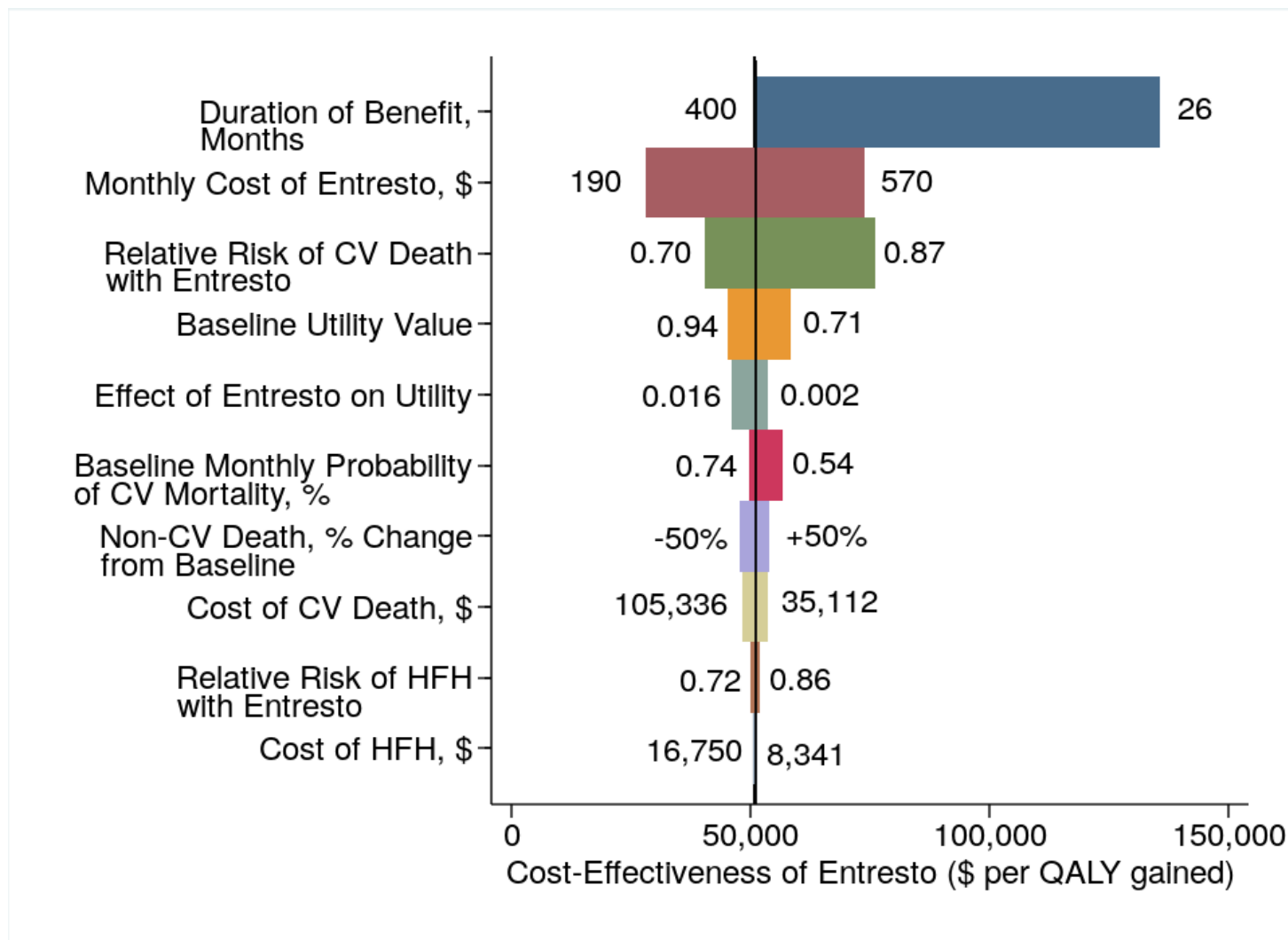
Results: Entresto Base Case

Entresto vs. ACE-Inhibitor: Entire Cohort

Arm	Heart Failure Hospitalizations	Life-years	QALYs	Cost (\$)	Incremental Cost-Effectiveness Ratio (\$/QALY gained)
ACE-Inhibitor	0.97	6.78	5.56	123,578	---
Entresto	0.90	7.41	6.13	152,716	50,915

Results: Entresto

One-way Sensitivity Analyses



Key Model Limitations

- Data of effectiveness derived from a single clinical trial
- Clinical trial effectiveness may not replicate real-world results
- Unclear long-term effects beyond trial durations
- High uncertainty regarding costs of CardioMEMS monitoring

Conclusions: CardioMEMS

- The estimate of the incremental cost-effectiveness ratio for CardioMEMS is approximately \$58,000 per QALY
 - Under most variations of assumptions, the cost/QALY remains less than \$100K
 - The cost/QALY goes above \$100K if it is assumed that the added benefits of the device end after 55 months

Conclusions: Entresto

- The estimate of the incremental cost-effectiveness ratio for Entresto is approximately \$51,000 per QALY
 - Under most variations of assumptions, the cost/QALY remains less than \$100K
 - The cost/QALY goes above \$100K if it is assumed that the added benefits of the drug end after 39 months



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Potential Budgetary Impact

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October 29, 2015

Disclosures:

I have no conflicts of interest.

Key review team members:

Rick Chapman, PhD

Budget Impact: Methods

- CardioMEMS

- Estimated # of Class III patients hospitalized annually:
 - ~287,000
- Assumed uptake: 25% by year 5
- Year 5 treated estimate: 359,000

- Entresto

- Estimated # of Class II-IV patients with reduced EF:
 - 2.2 million
- Assumed uptake: 75% by year 5
- Year 5 treated estimate: 1.7 million

Annual Budget Impact Threshold: Methods

- Based on calculations involving:
 - Target for overall health care cost growth (GDP+1%)
 - Number of new drug/device approvals annually
 - Contribution of drug/device spending to overall health care spending
- Serves as “policy trigger” for discussion of managing cost of new interventions
- 2015-2016 thresholds are \$904 million and \$603 million for drugs and devices, respectively

Budget Impact: Results at 5 Years

Intervention	Number Treated (thousands)	Annualized Budget Impact (Billions)	Discount to Match Annual Budget Impact Threshold
CardioMEMS	359	\$1.0	39.9%
Entresto	1,669	\$3.0	8.6%

Public Comments Received

- CardioMEMS

- Original candidate population size was based on hospitalization frequency—overestimated on a patient-level basis
- Uptake was overestimated; uptake was underestimated

- Entresto

- Revisit proportion of CHF patients who are Class I – PARADIGM-HF trial not representative
- Original CHF prevalence estimate (5.7 million) is outdated

Public Comments

Lunch

12:00 – 12:45



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Congestive Heart Failure

Questions for Deliberation

October 29, 2015

Comparative *Clinical Effectiveness*

Example Question

For patients with “**condition X**,” is the evidence “**adequate**” to demonstrate that the net health benefits of “**intervention A**” is greater than that of “**comparator B**”?

Yes

No

Care Value Example Question

Given the available evidence, what is the care value of “**intervention A**” vs. “**comparator B**”?

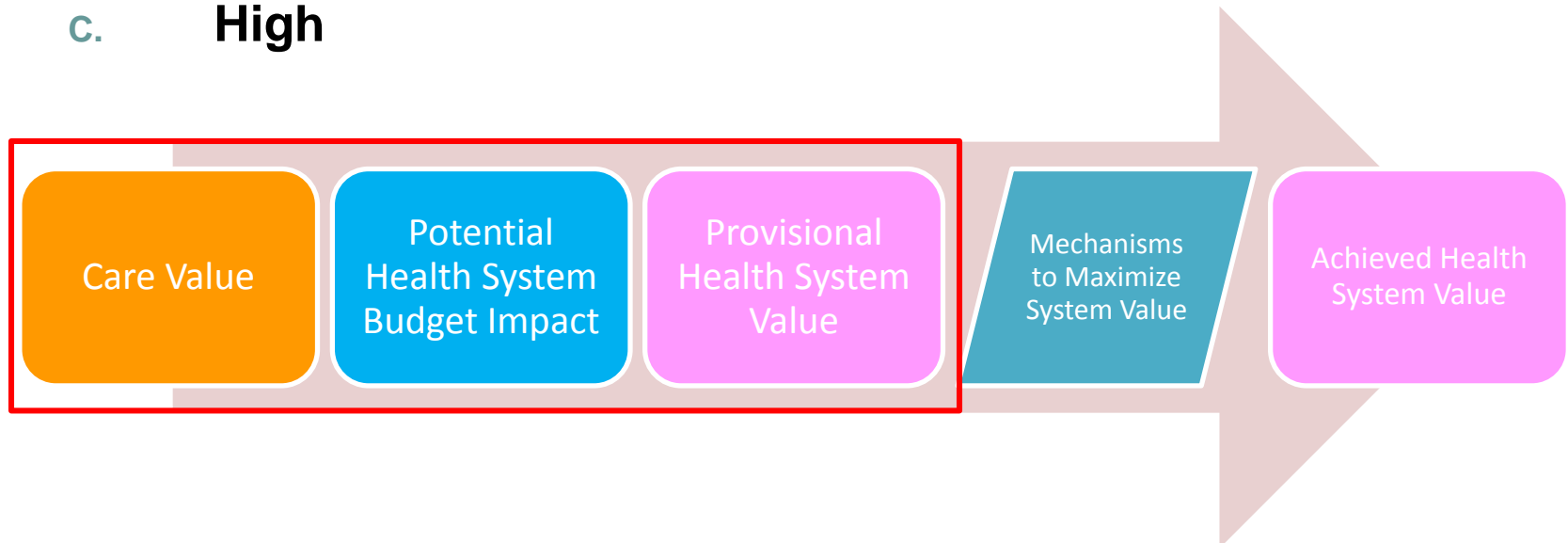
- A. **Low**
- B. **Intermediate**
- C. **High**



Health System Value Example Question

Given the available evidence, what is the **provisional health system value** of “**intervention A**” vs. “**comparator B**”?

- A. **Low**
- B. **Intermediate**
- C. **High**



Practice Question

Who is your favorite classic movie monster?

- A. Dracula
- B. Frankenstein's Monster
- C. The Creature from the Black Lagoon
- D. The Invisible Man
- E. The Wolf Man
- F. The Mummy

Entresto: Clinical Effectiveness

Q1. For patients with Class II-IV levels of CHF and reduced ejection fraction, is the evidence adequate to demonstrate that the net health benefit of **Entresto** is greater than that of **usual care with ACE inhibitors**?

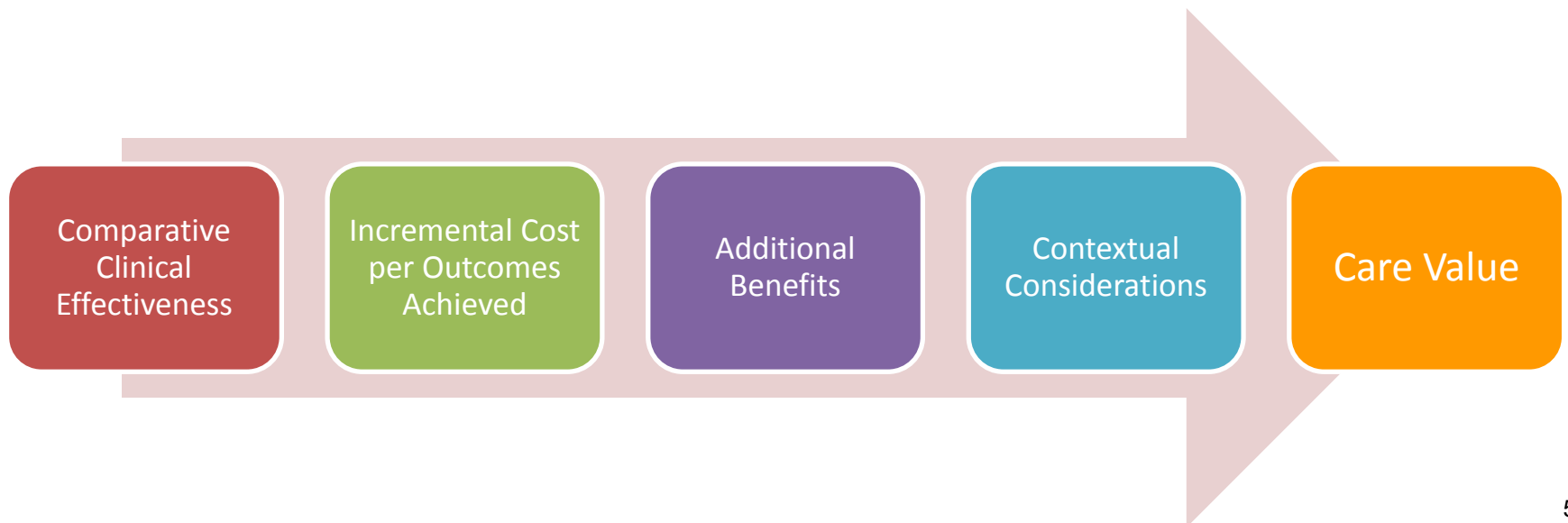
Yes

No

Entresto: Care Value

Q2. Given the available evidence for patients with Class II-IV CHF and reduced ejection fraction, what is the care value of *Entresto* vs. *usual care with ACE inhibitors*?

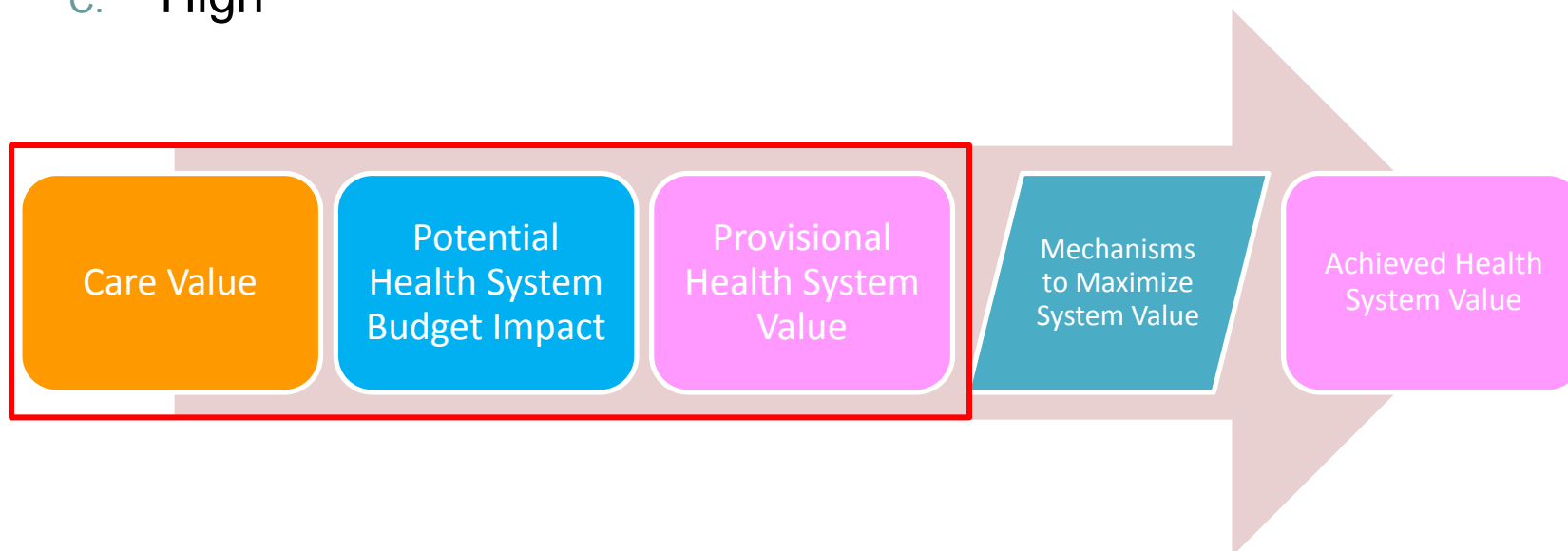
- A. Low
- B. Intermediate
- C. High



Entresto: Health System Value

Q3. Given the available evidence for patients with Class II-IV CHF and reduced ejection fraction, what is the provisional health system value of **Entresto** vs. **usual care with ACE inhibitors**?

- A. Low
- B. Intermediate
- C. High



CardioMEMS: Clinical Effectiveness

Q4. For patients with Class III CHF and a hospitalization in the prior 12 months, is the evidence adequate to demonstrate that the net health benefit of **CardioMEMS** is greater than that of *usual care*?

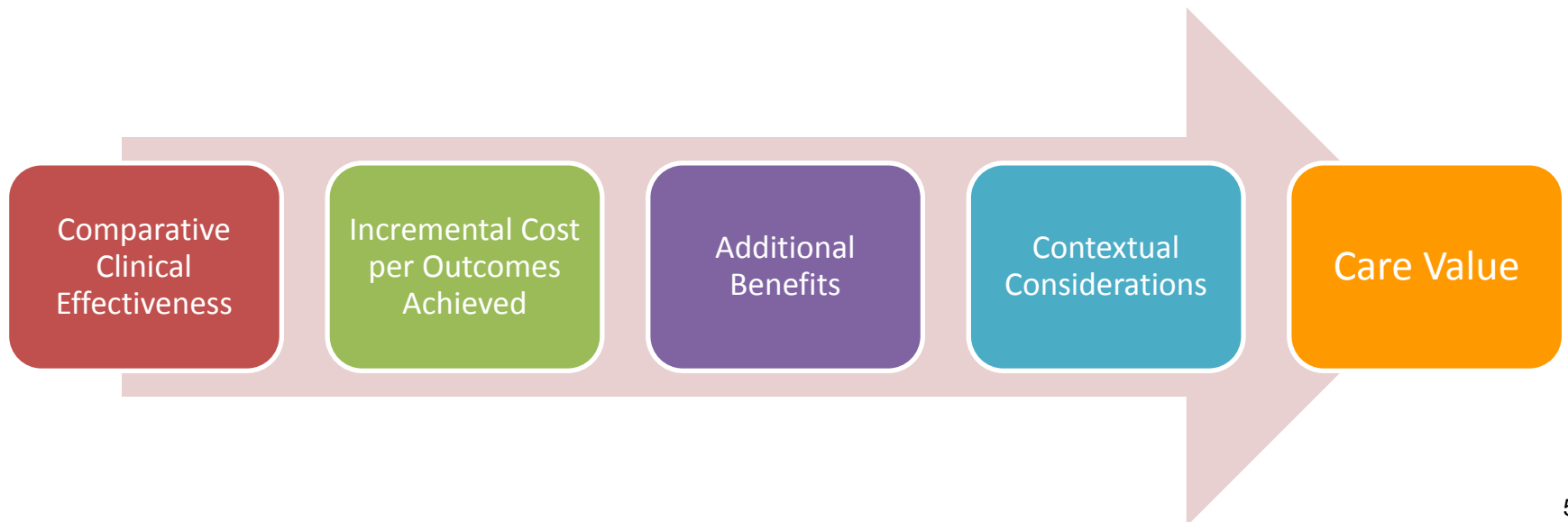
Yes

No

CardioMEMS: Care Value

Q5. Given the available evidence, for patients with Class III CHF and a hospitalization in the prior 12 months, what is the care value of **CardioMEMS** vs. **usual care**?

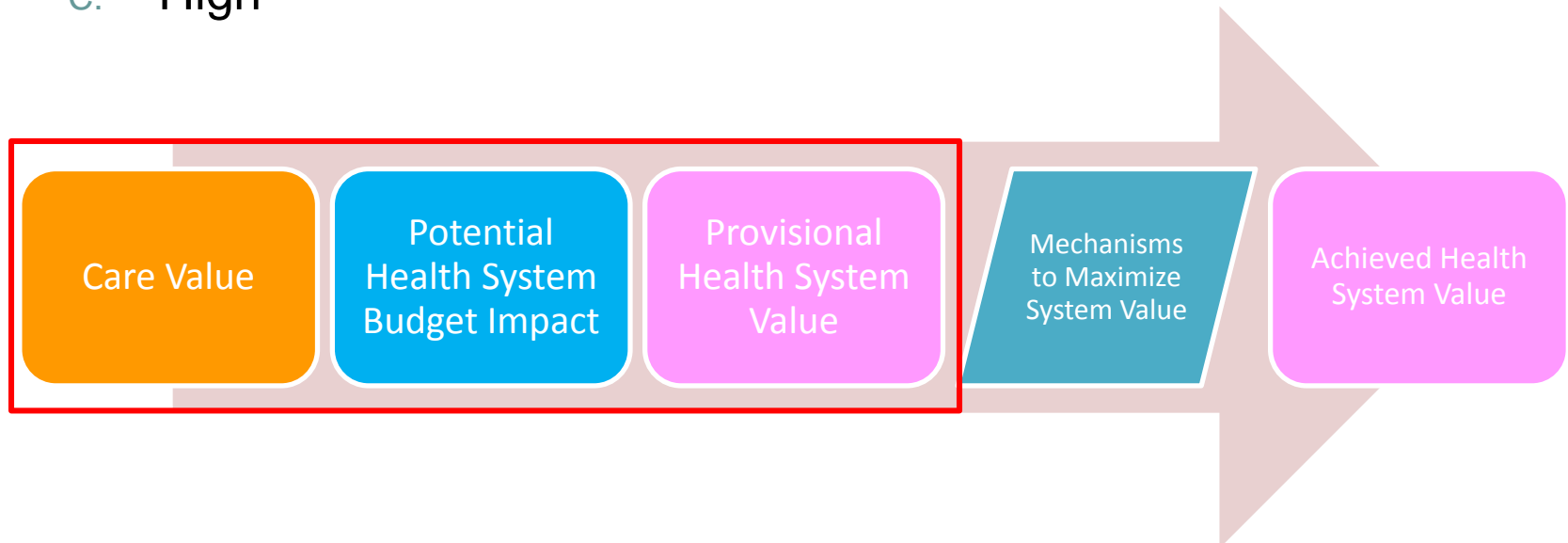
- A. Low
- B. Intermediate
- C. High



CardioMEMS: Health System Value

Q6. Given the available evidence for patients with Class III CHF and a hospitalization in the prior 12 months, what is the provisional health system value of **CardioMEMS** vs. **usual care**?

- A. Low
- B. Intermediate
- C. High



Break

1:30 – 1:45

Policy Roundtable Participants

- **Phil Adamson, MD**, Medical Director and Vice President for Medical Affairs, Global Research and Development, St. Jude Medical
- **Luanda Grazette, MD, MPH, FACC**, Associate Professor of Medicine, Division of Cardiovascular Medicine, Keck Medical Center of USC
- **Dipti Itchhaporia, MD, FACC**, Robert and Georgia Roth Chair of Cardiac Excellence and Medical Director of Disease Management, Hoag Heart and Vascular Institute
- **George Louie, MD**, Vice President and Medical Director, SCAN Health Plan
- **Glen Stettin, MD**, Senior Vice President – Clinical Research & New Solutions, Express Scripts
- **Tony Van Goor, MD, MMM, CPE, FACP**, Senior Director, Medical Affairs, Medical Director for Policy and Technology Assessment, Blue Shield of California

Reflections from CTAF Panel

Summary and Closing Remarks

Meeting Adjourned