Benefit-Risk Assessment and Comparative Effectiveness Research

- Are they really converging?-

…what does market access have to do with it…

Basel Biometric Society, September 25, 2012

Benefit-Risk & Comparative Effectiveness Seminar

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Acknowlegments & Disclaimer

Acknowledgments:

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- John Doyle PhD., Columbia Univ. & Quintiles
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Disclaimer:

The views and opinions contained in this presentation reflect those of the speaker, and should in no way be considered expressly those of the BBS nor of the contributors cited above.

A Bit of Background

In 5 years, all statisticians will be involved in drug safety

Stephen Evans, Eur. DIA biostatistics meeting, Venice, Italy 2002

In 5 years, all statisticians will be involved in health economics

David Sugano, Eur. DIA biostatistics meeting, Heidelberg, Germany 2006

2 burning issues facing the heads of biostatistics in pharma are drug safety and HTA

EFSPI Stats Leaders meeting, Berlin 2010

Agenda

1. Market and Political Environment:

   … the pharmaceutical and medical device industry´s need for a well-defined role for benefit-risk assessment and CER is driven by external environmental changes and internal challenges

2. Benefit-risk and CER in Product Development and Commercialization – Some common ground? - :

   … pharmaceutical companies have integrated benefit-risk into clinical development, but primary aim for registration remains the status quo and has led to suboptimal market access that CER should help to alleviate

3. Case Study – Rosiglitazone

4. Implications and Applications:

   … failure to demonstrate “real-world” evidence obtained through benefit-risk assessment and CER will result in cost-cutting measures and other restrictions to market access for new products and technologies

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Market and Political Challenges

The existing “Operating Business Model” in pharma is challenged by globally declining market growth rates, along with increasing costs and diminishing returns.

Market growth is driven primarily by specialist products, however high prices for speciality products have resulted in efforts by governments to limit volumes of prescription and price.

Benefit-risk assessment is considered a component part of *value-driven* drug development, and essential in achieving regulatory approval, whereas comparative effectiveness research is most commonly directed at reimbursement and payers as products are subjected to health technology assessments (HTAs) post-approval.

However, the important role both play in R&D and commercialization is often still not being fully recognized within companies.

Status Quo vis-a-vis HTA & Reimbursement

• Clinical trials are commonly designed with scientific objectives and endpoints to meet regulatory Market Authorization approval requirements. However, many drugs satisfying efficacy, safety, quality criteria and approved by Regulators, eventually fail to provide value to Heath Technology Assessment (HTA) Bodies and ultimately Payers. Pricing, Coverage & Reimbursement which must now be seen as integral parts of a "full" drug development process.

• HTA Bodies and Payers are today demanding more data to translate efficacy/safety data promise from clinical trials into expected effectiveness *vs.* current standard of care in clinical practice.

• This increasingly complex environment demands that pharmaceutical companies make critical decisions on how clinical trials should be better designed and equipped with the right tools to ensure that they will generate relevant and measurable data for key healthcare stakeholders.

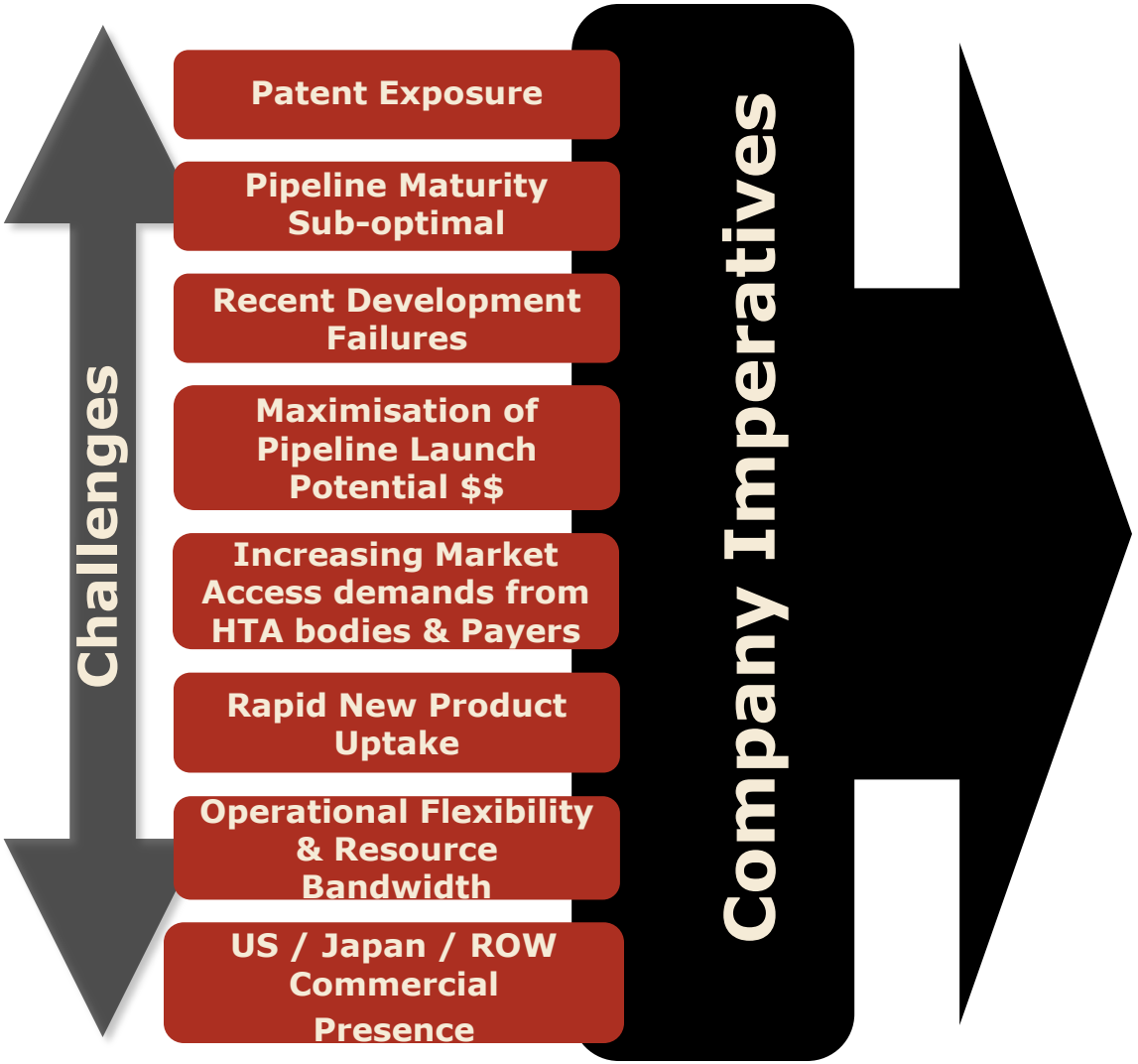
• Companies are then able to provide evidence-based value propositions and generate data needed for pricing agreements. In addition, they have then the evidence to demonstrate their products' superior health outcomes and benefit-risk profile against comparators, and thus optimize commercialization

Key Message

An Organization needs to anticipate and react early to potential future requirements to alleviate tensions between clinical outcomes and HTA Bodies'/Payers' expectations.

US landscape is changing with American Recovery and Reinvestment Act of 2009

Challenges & Strategic Imperatives for the Industry



Critical Success Factors

- Maintain top line growth
  - Partner/Acquire (Companies, Compounds, Brands)
  - Target high growth CNS sectors / Diversify
  - Influence clinical guidelines
- Cut costs to improve short term earnings
  - Administration
  - Sales & Marketing resource
  - Build flexible resource model

Optimize Portfolio Strategy

- **Primary vs. secondary care**
- **Maximise commercial potential of pipeline assets**
- **Incorporate Market Access stakeholders perspectives alongside traditional KOLs in guiding R&D decisions and priority setting**

- Globalise business
  - Strengthen US / Japan position
  - Global Brands / molecules

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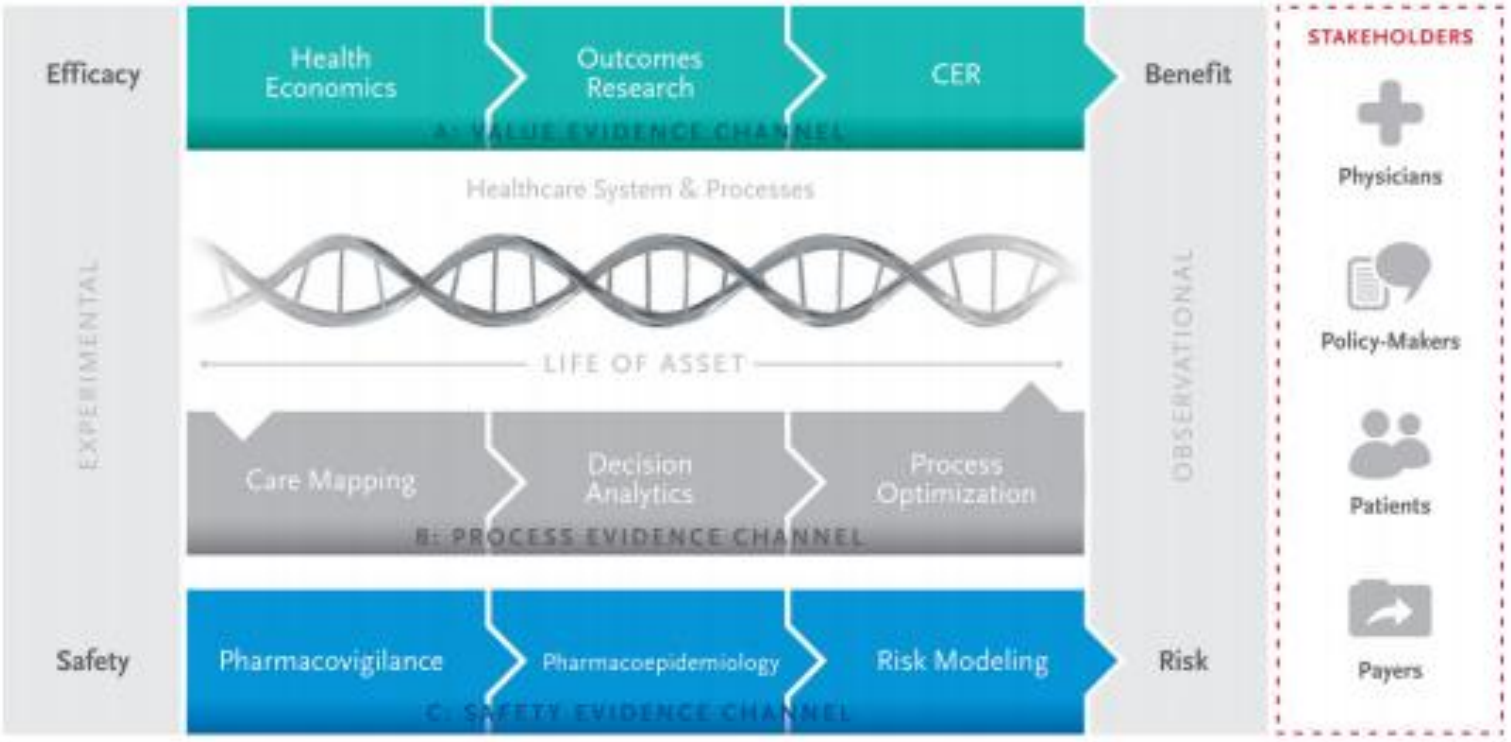
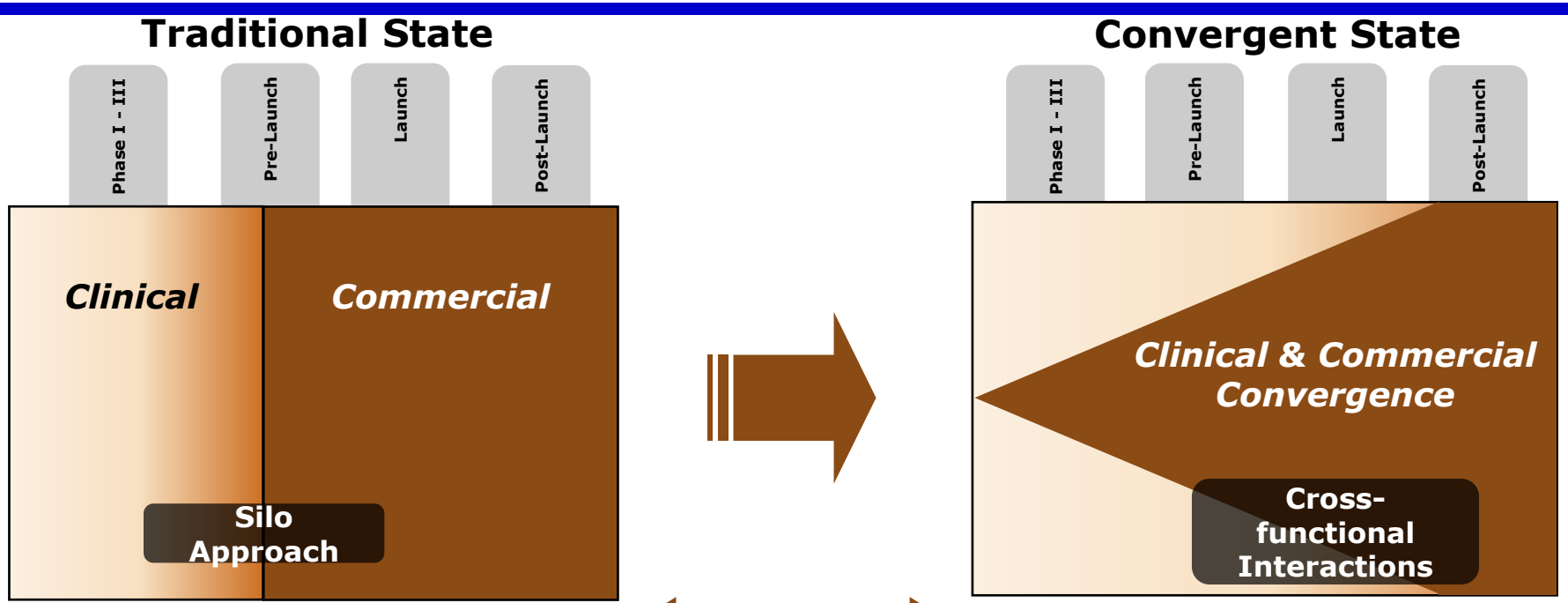
Benefit-Risk and CER serve the value and safety channels

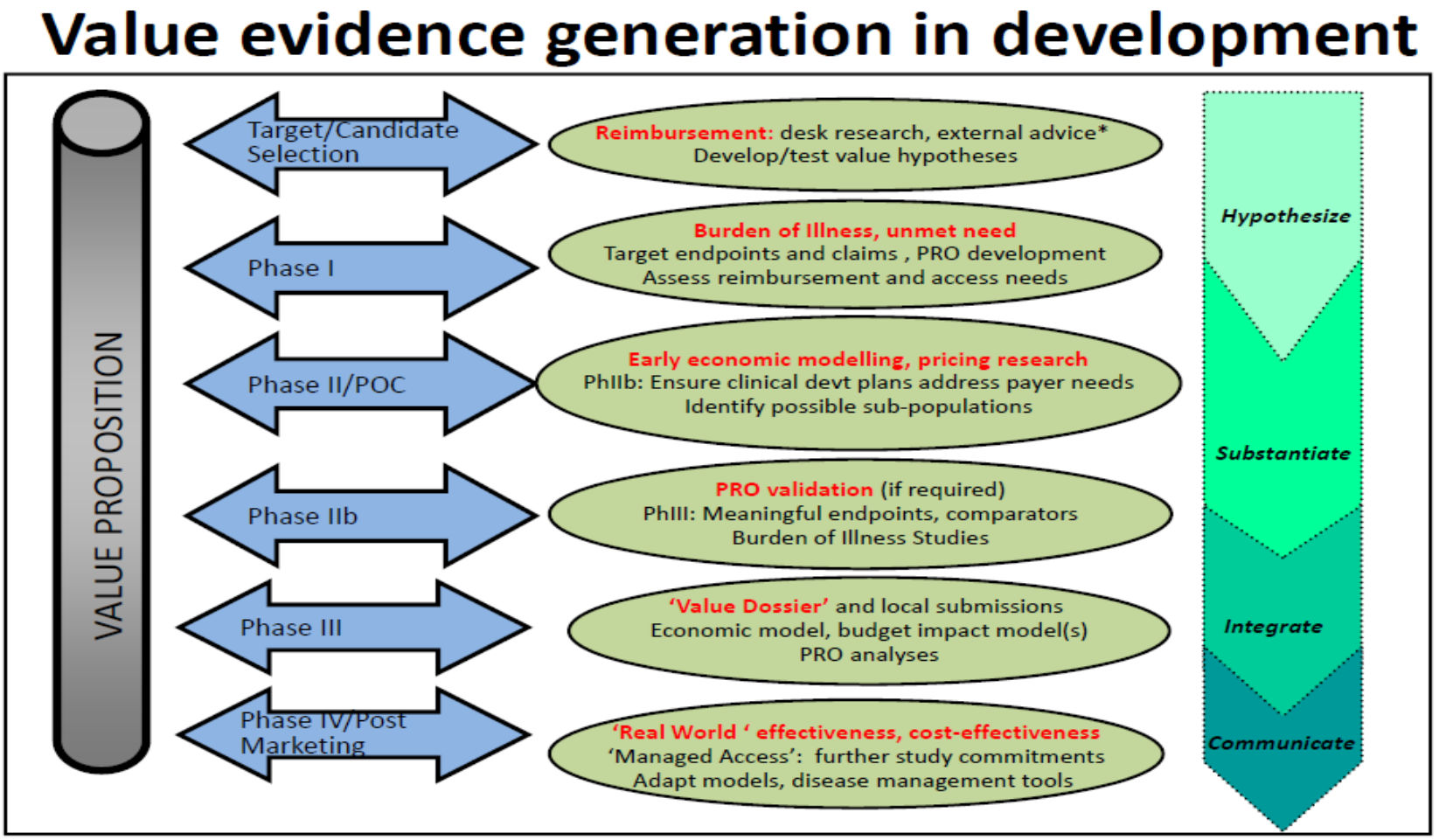


R&D Alignment With Payer Perspectives Is Sub-Optimal Across The Industry



Integrating Health Economic input early in clinical development is important to optimize value in the marketplace.

A Robust Product Value Proposition is Critical in Development



Value Evidence Generation during Product Development

- Planning a variety of studies
  - Burden of illness (observational)
    - Understanding epidemiology
- Randomized Controlled Trials (interventional)
  - Design considering regulatory and payer requirements
- Chart reviews (observational)
  - E.g. Resource utilization
- Existing database analyses (observational)
  - E.g. Pharmacovigalence

Lack of therapeutic innovation cannot be compensated by promotion anymore……

- Ultimate success in the market place is driven by the relevance & strength of clinical & economic evidence provided to payers
- Cost-effectiveness evidence requires relevant and persuasive clinical evidence, often requiring a comparison against standard care
- Pricing & Market Access challenges are often directed at the clinical evidence base
- Payers' clinical & economic evidence needs should be considered in constructing the clinical development plan well before Phase III
- DATA, DATA, DATA

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Some causes of uncertainty and evolving data

- BR assessment and corresponding decision must synthesize numerous endpoints and reconcile variable data quality…can compromise the transparency, objectivity & rigor.
- Implied linkages between short-term effects (e.g., CD4, HbA1c) and their purported sequelae.
- Benefit and risk effects are analyzed separately and statistically (clinical relevance implied).
- Main way to address uncertainty: more data!

Health Outcomes Model: connecting the dots

Example from Type 2 diabetes

All RCTs	Most RCTs	Some RCTs	Few RCTs
Drug effect	**Intermed outcomes**	**Clinical outcomes**	**Final outcomes**
• Blood glucose control	• Retinopathy • Nephropathy • Neuropathy	• Blindness, • End stage renal disease • Amputation	• Survival • Death
Pre-approval	**Post-approval**		**UKPDS, Epi studies**

Framing the CBR Assessment: clinical/regulatory context

- *Glyburide* (approved 1984):
  - Benefit: Glucose control, but tends to be less “durable”
  - Risk: hypoglycemia, weight gain
- *Metformin* (approved 1995):
  - Benefit: Glucose control; without hypoglycemia and weight gain
  - Risk: Lactic acidosis?
  - First-line pharmacotherapy
- *Rosiglitazone* (approved 1999):
  - Benefit: Superior to placebo, non-inferior to glyburide
  - Risk: hepatotoxicity? (troglitazone pulled from market); edema
  - 2nd in class

What changed between 1999 and 2007?

- In 2007:
  - 5-year data: more durable glycemic control vs other drugs
  - hepatotoxicity seen in troglitazone no longer a concern for Avandia
  - CHF confirmed…MI/CV death?

Incremental Net Health Benefit (INHB)

- Aggregate an array of outcomes using a metric that combines *quality of life (utility) and length of life.*

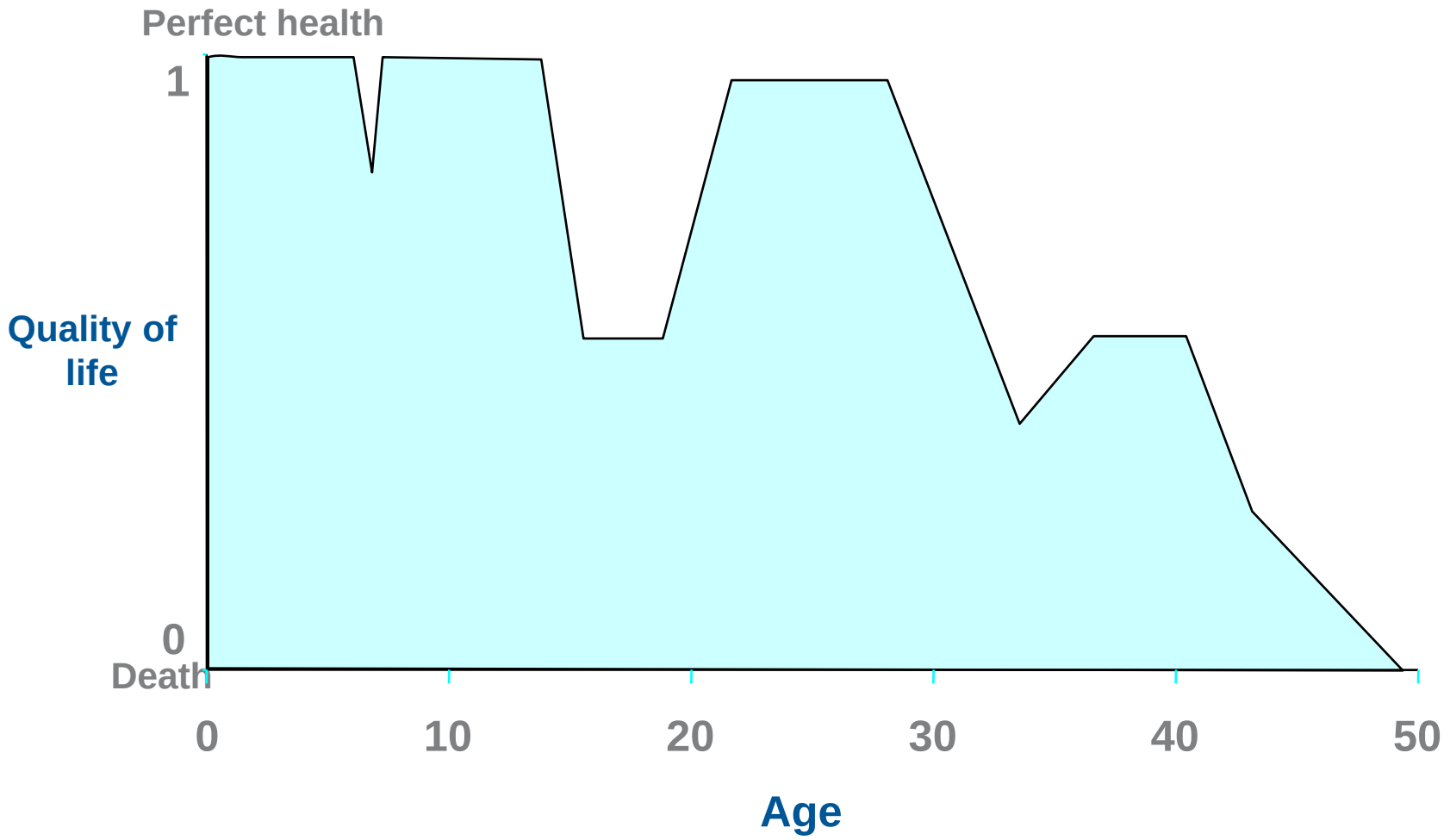
  - Quality-adjusted life-year (QALY)

- Net Health Benefit = $\Sigma_{Benefits} - \Sigma_{Risks}$

- Incremental NHB = $NHB_{(drug\ A)} - NHB_{(drug\ B)}$

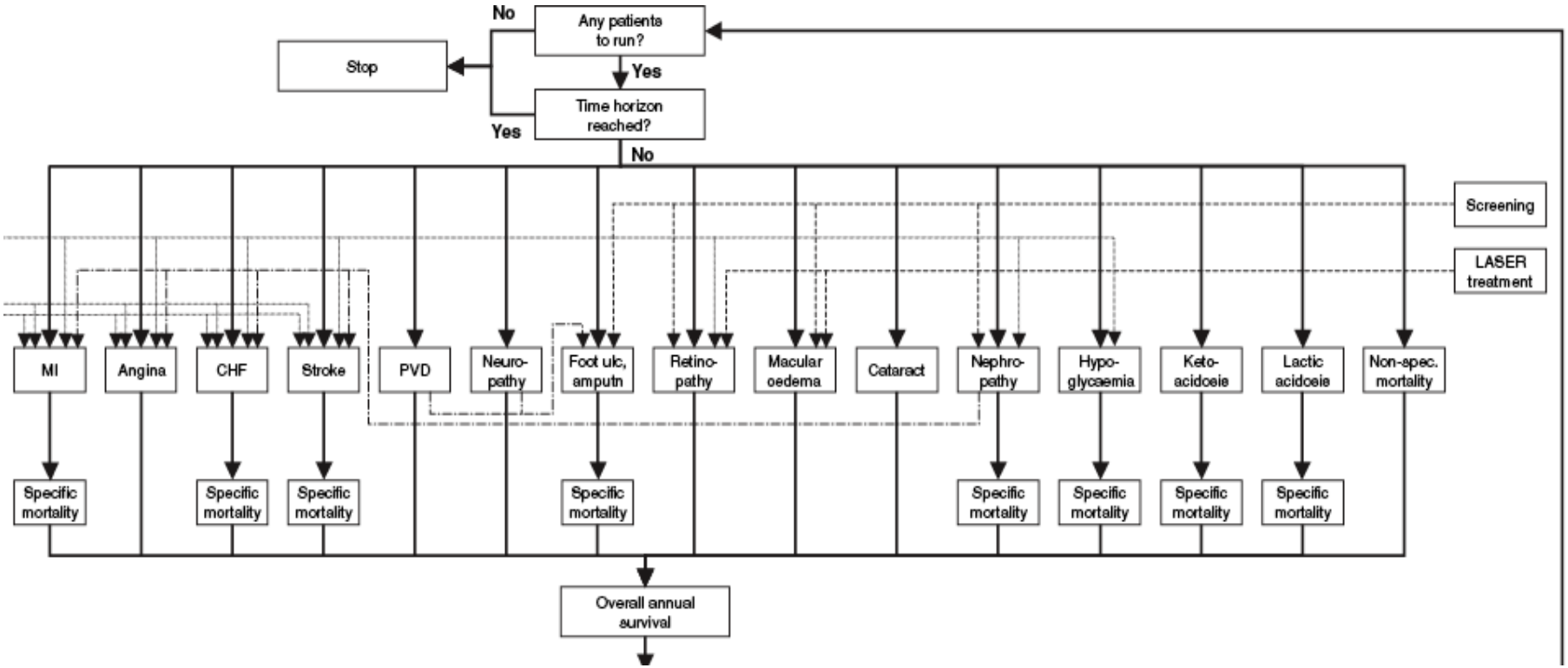
J Cross & L Garrison. Office of Health Economics Aug 2008

Utility over a Patient's Life Cycle



Methods: Model Overview

- CORE-IMS diabetes model



Palmer AJ. *Curr Med Res Opin* 2004.

Methods: Sources for Key Model Inputs

Model parameter	1999	2007
Glycemia (HbA1c)	Phase 3 trials	ADOPT study
Utilities	UKPDS (EQ-5D)	UKPDS (EQ-5D)
P(severe hypoglycem.) **P(die)**	Phase 3 trials Hospital-based retrospective study	ADOPT study Hospital-based retrospective study
P(fulmin. liver failure) **P(die)**	Troglitazone reports FDA testimony	N/A
P(pulmonary edema)	Phase 3 trials Retrospective studies	N/A
P(CV death)	N/A	FDA meta-analysis

Results, 1999

1999	*Life-Years*			*QALYs, discounted*		
	RSG	GLY	PBO	RSG	GLY	PBO
Benefit	12.316	12.626	11.674	6.740	6.911	6.361
Harms	0.003	0.001	0.000	0.003	0.001	0.000
NB	12.313	12.625	11.674	6.737	6.910	6.361
INB	--	-0.312	0.639	--	-0.173	0.376

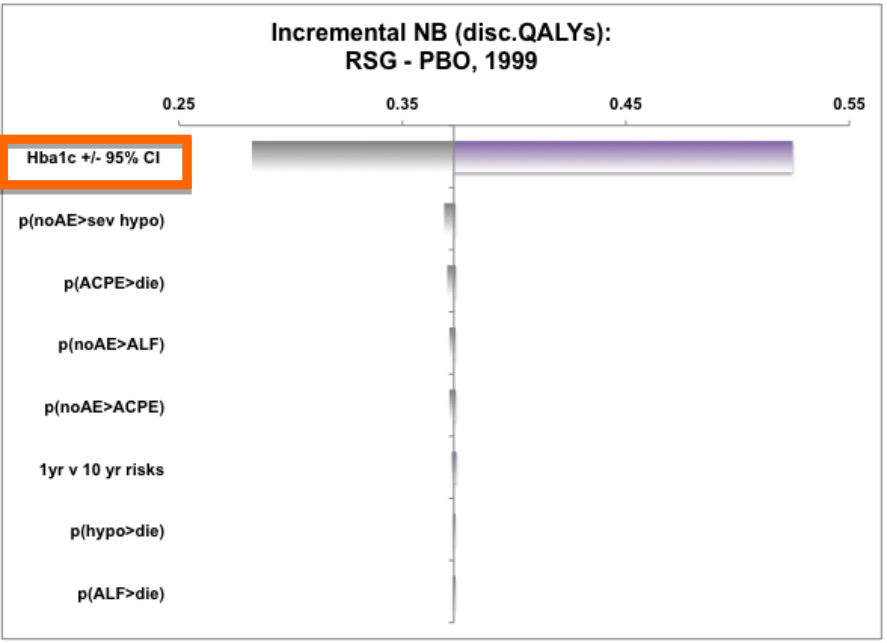
INB: Incremental net benefit.
INB >0 favored RSG. INB <0 favored comparator.

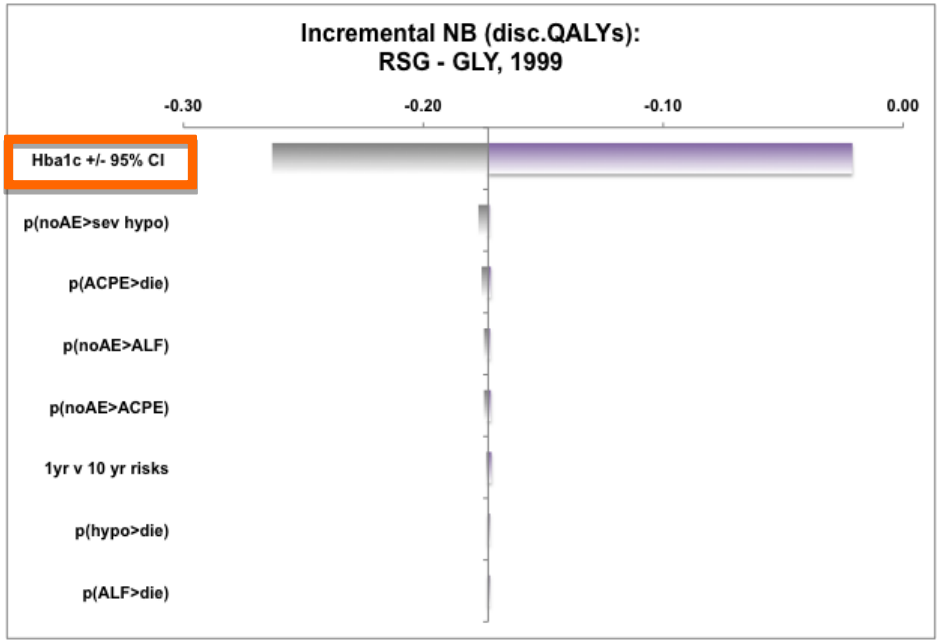
Results, 2007

2007	*Life Years*			*QALYs, discounted*		
	RSG	GLY	MET	RSG	GLY	MET
Benefits	14.651	14.379	14.574	7.937	7.821	7.903
Harms	0.051	0.001	0.000	0.026	0.001	0.000
NB	14.600	14.378	14.574	7.911	7.821	7.903
INB	--	0.222	0.026	--	0.091	0.009

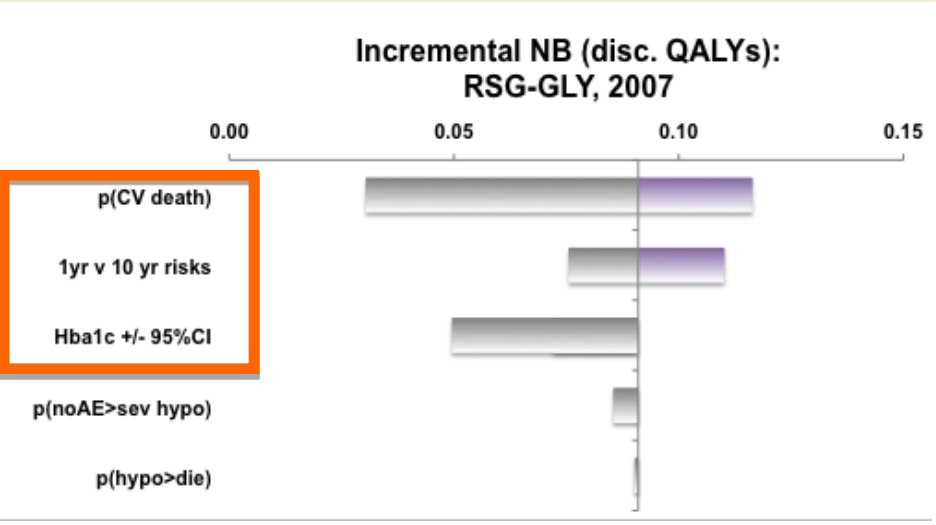
INB: Incremental net benefit.
INB >0 favored RSG. INB <0 favored comparator.

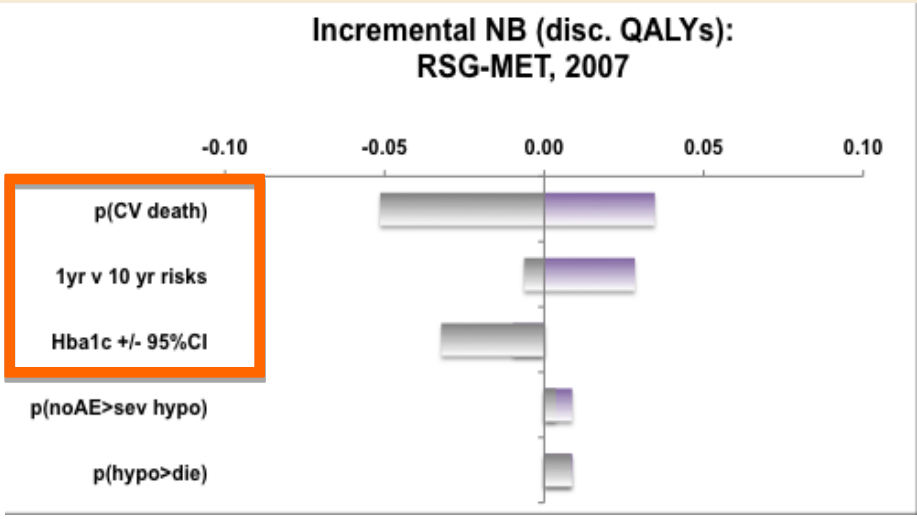
Sensitivity Analyses from 1999 Data





Sensitivity Analyses from 2007 Data





Conclusions: transparency of assumptions

- Rate of rise in HbA1c was linear. (UKPDS, FDA)
- CV events while on glyburide or metformin were disease-related, not drug-related. (labeling)
- Did not evaluate combination therapy.
- Probability of harm was not time-varying.
- Risk of adverse events only for 5 years.(UKPDS)
- Only fatal adverse events modeled (excluded harms such as bone fracture and lactic acidosis).

Conclusions: evolving data and uncertainty

- One can explore the effect of uncertainty in individual parameters and in aggregate on overall CBR. Goes beyond trial context.
- The FDA might have reconsidered initial (1999) approval for monotherapy given efficacy data? Would have sought longer trials?
- Given uncertainty from CV risks, findings upheld past ADA guidelines recommending metformin as the first-line monotherapy.

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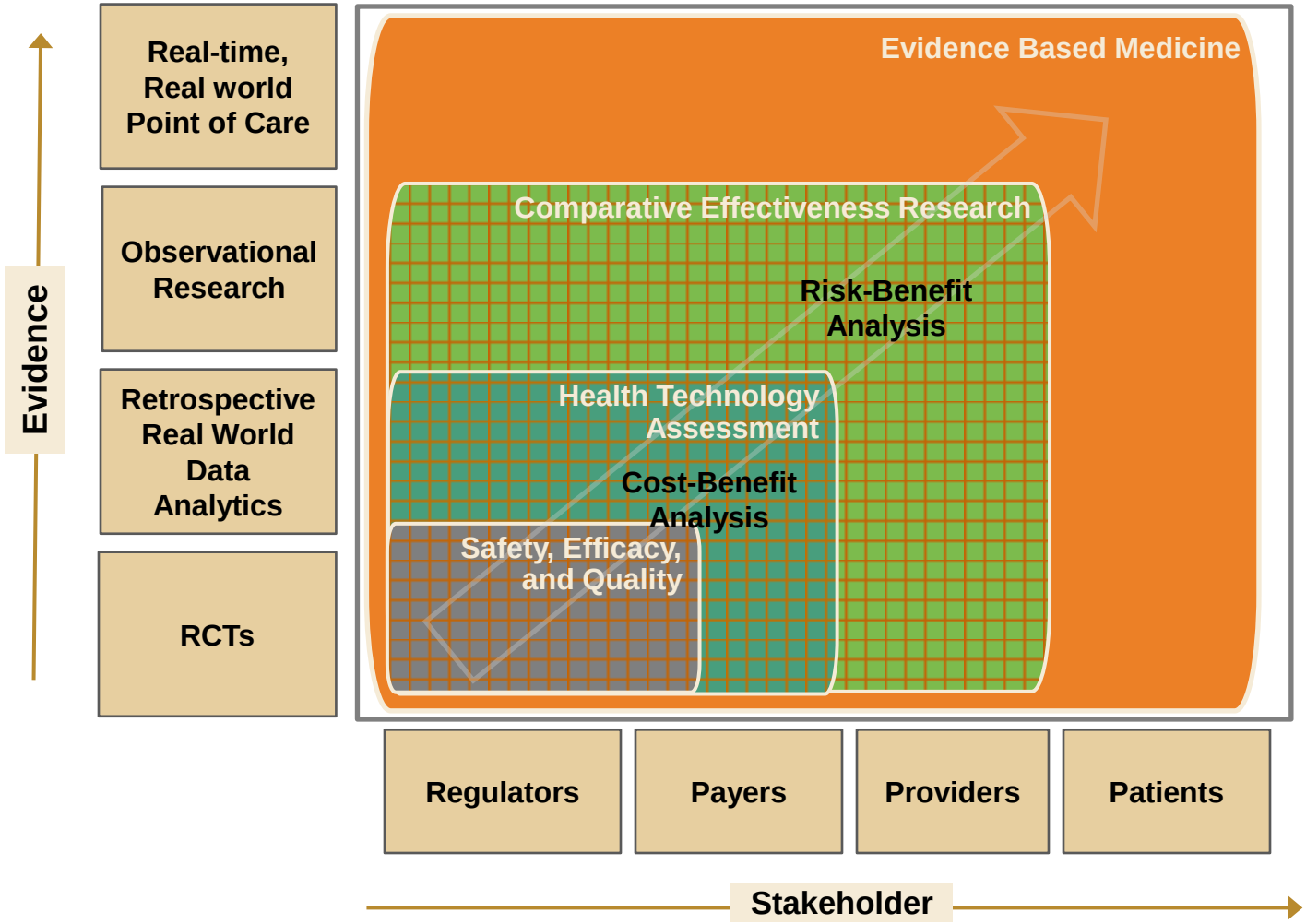
Evidence will always remain the primary foundation



Comparative Effective Research – Where is it going?

Patient Fears

- Restriction of patient access to expensive treatments
- Allowance of government to use CER to make cost-benefit calculations and focus on cost containment data rather than clinical evidence

Recent Examples

New Zealand

- New Zealand's CER Agency, Pharmac took 5 years to approve the use of the anti-cancer drug Herceptin

Britain

- NICE denied approval for several cancer drugs widely available in other countries because of cost

U.S.

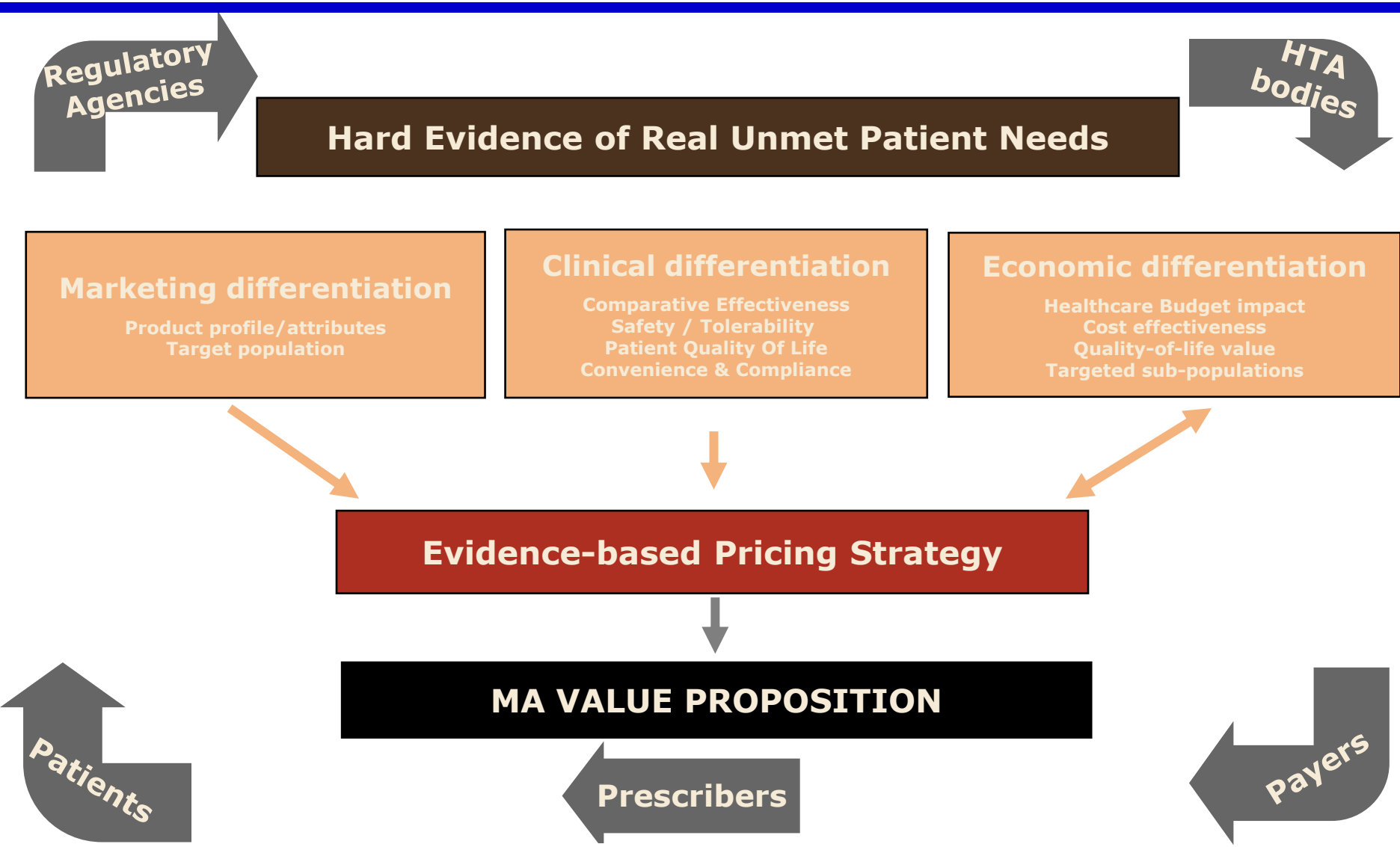
- FDA approved Avastin in 2008 but it revoked the indication for advanced breast cancer, claiming it does not extend life long enough overall
- Provenge initially approved for Medicare coverage for "on label" use only

The Unknown

- Cost-effectiveness decisions are prohibited under PPACA from being used as sole basis for denying coverage in federal programs, and
- Cost-effectiveness thresholds for coverage are barred
- PCORI may not use a "dollars-per-quality adjusted life year . . . as a threshold"
- A patient centered approach to generating evidence would support personalized medicine
- More effective treatments may increase the overall costs, not necessarily reduce costs

Build A Consistent Product Value Proposition

Combining Various Aspects Into A Single And Consistent Entity



Several initiatives are already in place

INITIATIVES TO DEMONSTRATE REAL-WORLD VALUE:

STROBE (Risk-Benefit)
- **22-point checklist of factors to include in an accurate and complete report of an observational study**

OMOP (Risk-Benefit)
- **Public-private methods development and testing consortium taking a 2 tiered approach**

ISPE (Observational/Pharmacoepidemiologic)
- **Address protocol development, responsibilities, study conduct, communication, adverse event reporting, and archiving**
- **An earlier FDA document had similar objectives**

Sentinel Initiative (Safety)
- **Focused on real world long-term safety and risk data based on retrospective analysis of claims data**

CMS (Evidence of Value)
- **Manifested by its national coverage decisions that recommend 'coverage with evidence development'**

Conclusion

Benefit-Risk and Comparative Effectiveness Programs for Regulators and Payers should both:

- **Foster a strong collaboration between Clinical R&D, Drug Safety, Health Economics and Marketing with strong biostatistics (quantitative) support in all areas**
- **Define clear roles and responsibilities to make the most effective use of expertise, skills and resources**
- **Contribute more case studies on how methodologies are best applied and influence decision making**

Conclusion (continued)

Benefit-Risk and Comparative Effectiveness Programs for Regulators and Payers should both:

- **Enable effective communication of value evidence generation activities across the whole product life-cycle**
- **Provide for early engagement and cross-functional alignment on regulatory and market access hurdles**
- **Be flexible and adaptable to meet a complex and evolving global market environment and still meet needs of patients with best available cost-effective care**

References

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- **Can modeling of health outcomes facilitate regulatory decision making? The benefit-risk tradeoff for rosiglitazone in 1999 vs. 2009** Cross JT et al. *Clin Pharmacol Ther* 2011. 89:429-36.

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Thank you for your attention