24 September, 2015
Boston ISPOR

Adaptive Pathways: What's in it for Payers?

Mark Trusheim
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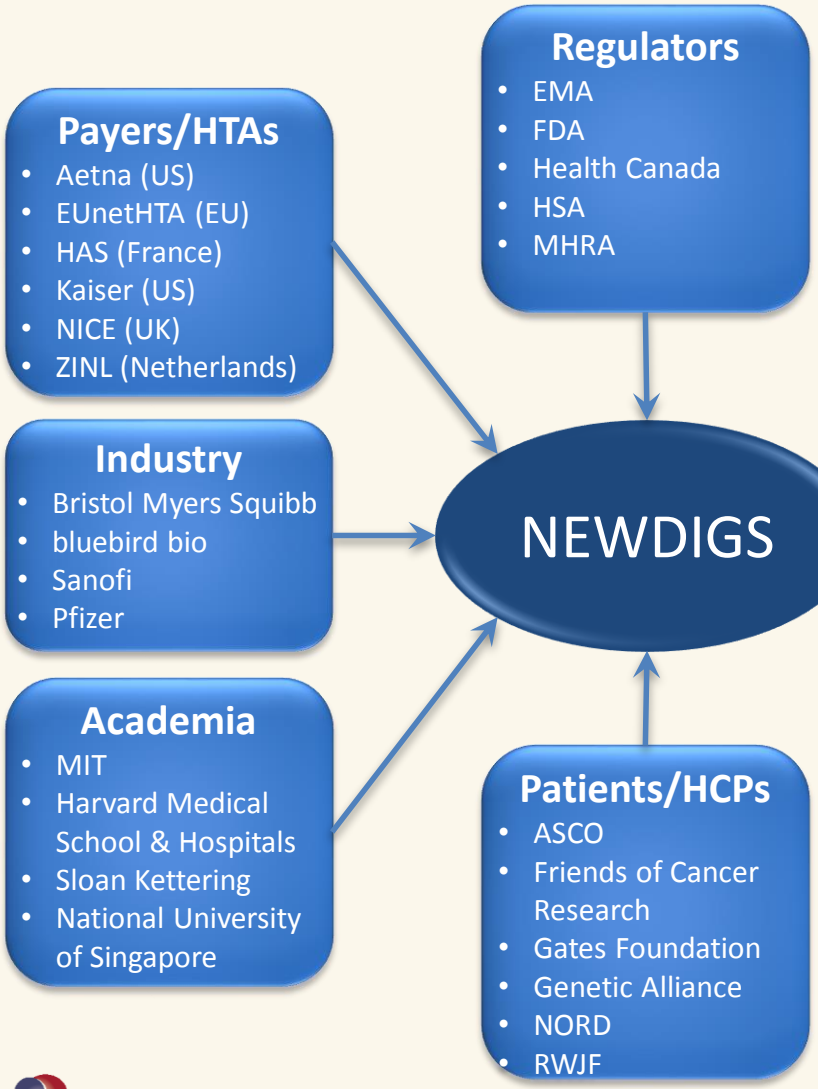
Varied Background, Distinctive Perspective

- Academic: Chemistry/Stanford, Management (IT, Finance)/MIT
- High Tech: Wang Labs, Kenan Systems-put first AI system in international banking & large data mining (Sold to Lucent $1.4B)
- Monsanto:
  - Searle Managed Care Marketing
  - Growth Enterprises (>60 “start-ups”)
  - Monsanto Health Services: Patient & Wellness Management
  - Genomics: Director Alliance Web & Co-President Cereon Genomics ($1.5B deals)
- Diagnostics Start-up: Biochemical Profiling
- Board & President: Mass Biotech Council
- Special Government Employee, FDA Office of the Commissioner
- MIT Visiting Scientist & EIR
- Co-Bio Consulting

Moving Beyond Siloes to Serve Patients: The NEWDIGS Safe Haven Incubator Environment



Critical Enablers:

- Common Goal (Improving Patient Lives)
- Neutral Ground (MIT)
- Confidentiality (Chatham House Rules)
- Transparency (Data driven, Documented)
- Collaborative Work (Workshops, Models, Studies)

Stakeholder Relationships & Actions

Numerous assets reviewed since 2011:

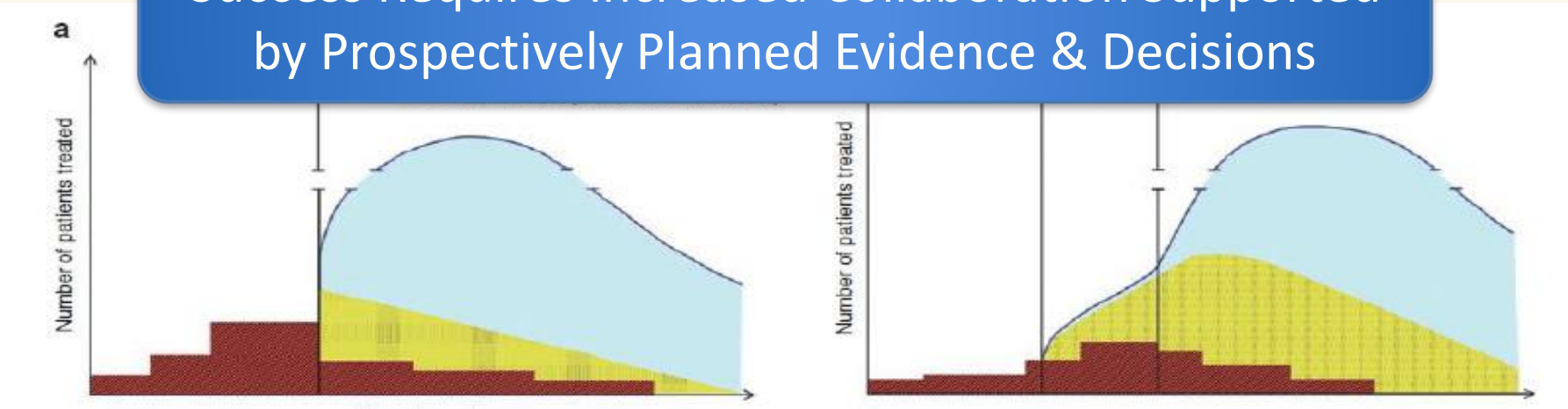
- 15 assets nominated by 9 companies
- 14 assets evaluated in scenario design sessions
- 6 assets presented at 2 or more workshops

Note: Partial list of collaborators

Adaptive Pathways Shift
Evidence Timing, Amount and Use

- Evolving license over therapeutic life span
- Clinical Trial: adaptive to basket to N of 1
- Real World Data 'fit for purpose' for policy decisions
- Patient population variability understood and tied to clinical population outcomes
- Patient preferences explicitly accommodated

Success Requires Increased Collaboration Supported by Prospectively Planned Evidence & Decisions



MIT CBI, Eichler et al (Mar 2012) CP&T 91(3)426:437

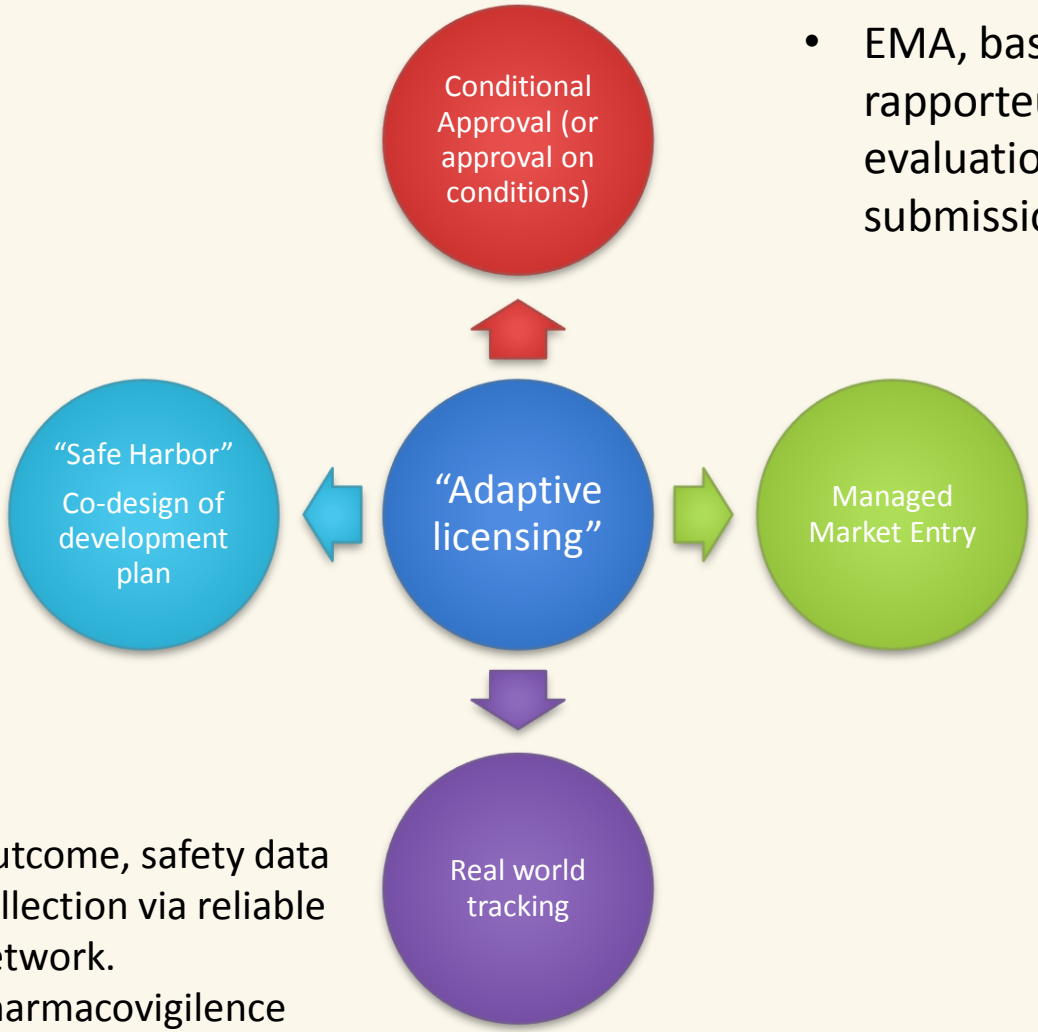
What Will Change with Adaptive Pathways?

Transition from …

Magic Moments	→	**Life-span Management**
Prediction	→	**Monitoring**
RCT Only	→	**Toolkit for Evidence Generation**
One size fits all	→	**Benefit/risk optimization**
Focus on Licensing	→	**Focus on Patient Access**
Open Utilization	→	**Managed Utilization**

Hans-Georg Eichler, DIA 2014

Key elements of the EMA Adaptive Licensing Concept



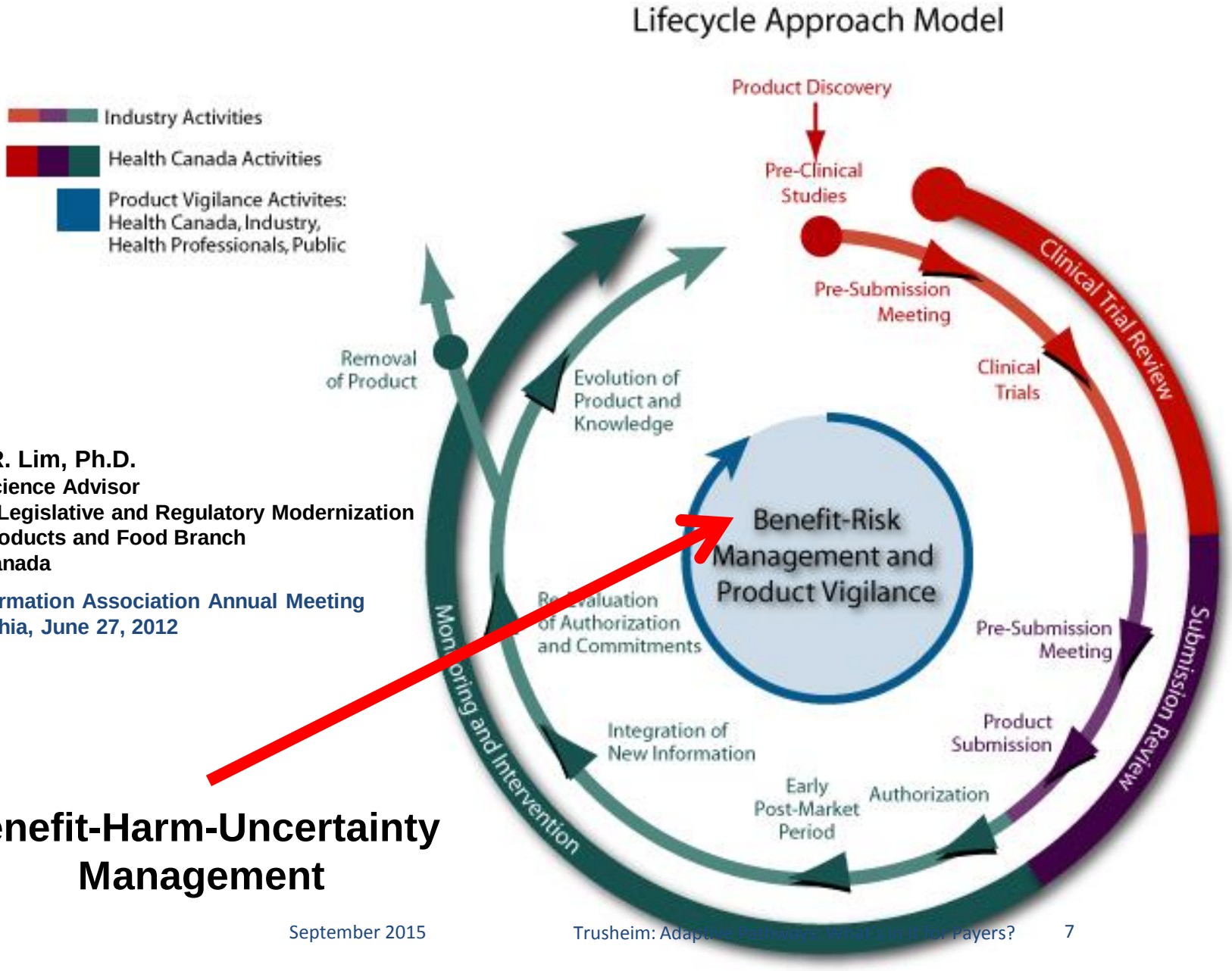
- EMA, based on rapporteur (MHRA) evaluation of submission

Stakeholders:
-Sponsor
-Regulator
-HTA
-Patients

- Prescribing managed
- sponsor reimbursed

- Outcome, safety data collection via reliable network.
- Pharmacovigilence legislation

HC's Vision for Modernized Regulatory Oversight



Robyn R. Lim, Ph.D.
Senior Science Advisor
Office of Legislative and Regulatory Modernization
Health Products and Food Branch
Health Canada

Drug Information Association Annual Meeting
Philadelphia, June 27, 2012

Benefit-Harm-Uncertainty Management

Adaptive Pathways Misconceptions

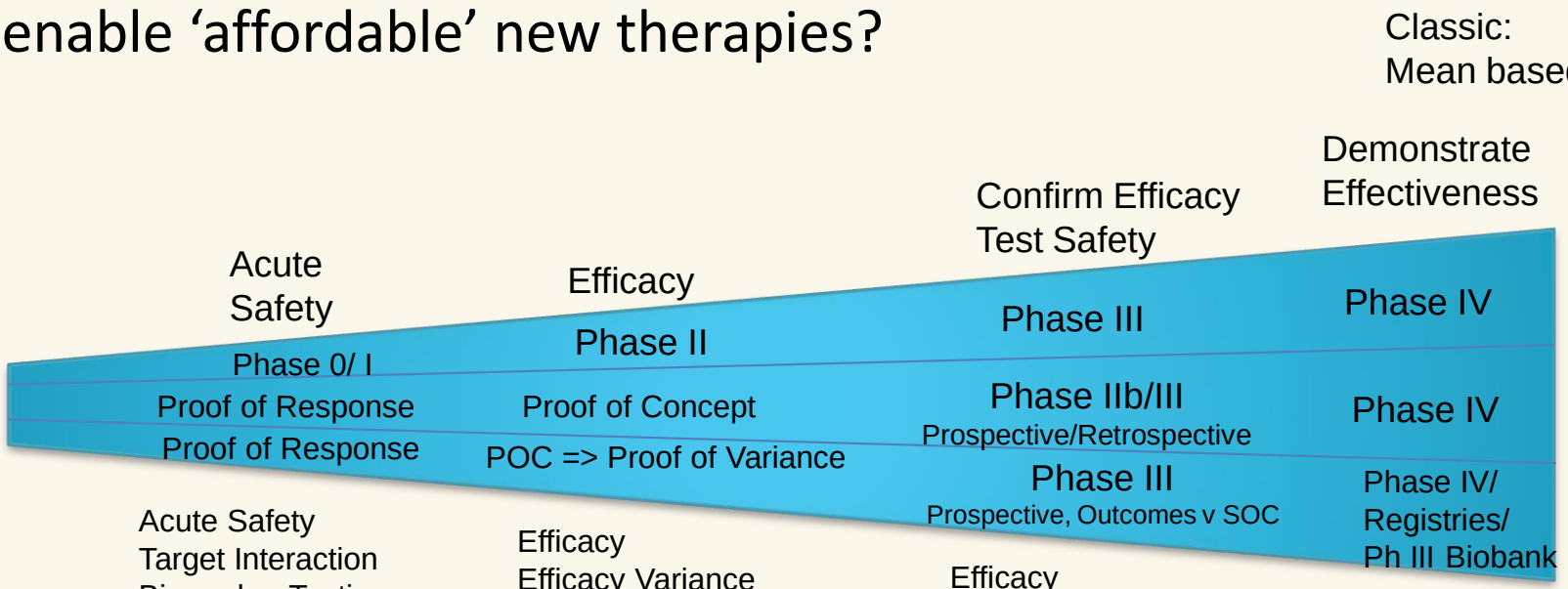
- MYTH: Evidence standards are lower
  - » Actually increases evidence over time
  - » Multiple decision points change timing of patient access
  - » Quid pro quo for developers: Earlier market access in exchange for continued monitoring and label changes based on that monitoring
- MYTH: Development is fast and at lower cost
  - » ONLY to FIRST decision. May increase if ongoing monitoring does not leverage payer & clinical systems
  - » Entire clinical development program through indication roll-out & surveillance AGREED early
- MYTH: Patients gain unfettered early access
  - » Early patients must likely participate in tracking, registries and observational studies with associated informed consent
  - » REMS with 'teeth'

Adaptive Pathways Advantages

- Payer Advantages
  - **Influence** choice of valuable clinical endpoints BEFORE clinical trials
  - **Systematic** clinical utility evidence over time
  - **Early estimates** of total budget impact & access approach
  - **Appropriate** early patient access and public health impact
  - **BUT**: leaves open issue of willingness/ability to pay for greater population health VS. providing current health at lower cost
- Regulator Advantages
  - **Visibility** to life span development, including real-world data
  - **Improved understanding** of benefit/harm/uncertainty in real world populations
  - **Higher confidence** in appropriate access in real world settings
  - **More sensitive titration** of refine label and use over time

The Alternative Evidence Path: Learn "Everything" Before Approval & Access

Will longer, larger RCTs really demonstrate clinical utility in 'real' populations and enable 'affordable' new therapies?



Degrees of Adaptiveness: The Adaptive Licensing Score

- Needed to compare relative adaptiveness of various programs
- Composed of INPUT factors and OUTPUT (outcomes) factors
- INPUT factor categories
  - Adaptive Learning – prior to regulatory approval
  - Serial, Adaptive Licensing
  - Access graduated over time
  - Communications and controls
- OUTPUT factor categories
  - Learning – after regulatory approval
  - Regulator/Payer/Prescriber metrics- Appropriate use
- Each feature scored as 1 point
- Higher scores indicate higher adaptive licensing approach

AL Score **Input Factors** for Gilenya and Zelboraf

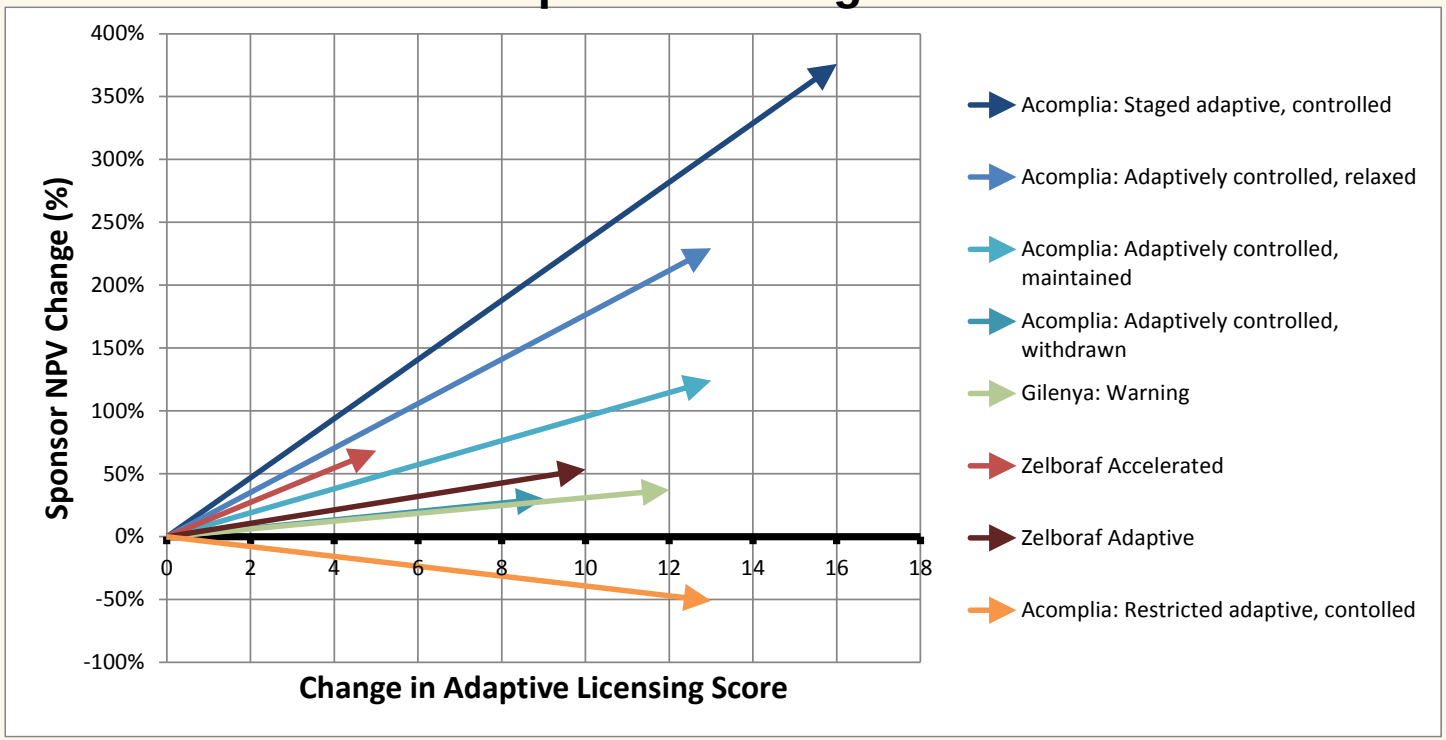
Input Factor / Attribute	Gilenya		Zelboraf		
Learning	**Actual**	**Adaptive Licensing**	**Traditional**	**Actual**	**Adaptive Licensing**
Prospectively planned post-authorization trial(s)	0	1	0	0	1
Clinical confirmation of efficacy based on surrogate endpoints	0	1	1	1	1
Confirmation at traditional significance level of efficacy based on relaxed significance	0	0	0	1	1
Registry/observational study	1 (post-marketing)	1 (post-initial authorization)	0	0	0
Expanded access program	0	0	0	1	1
Licensing					
Periodic benefit/risk reassessments	0	1	0	0	0
Preplanned serial authorizations	0	1	0	0	1
Access					
Restricted to on-label population	0	1 (based on disease severity)	1 (test positive for mutation)	1 (test positive for mutation)	1 (test positive for mutation)
Staged expansion of patient populations	0	1	0	0	0
Controlled prescriber or facility access	0	1 (Years 0-5)	0	0	0
Communication and Controls					
Established educational support for patients and prescribers	0	0	0	0	0
Timely communication of new and emerging product information to patients and prescribers	1 (Years 0-5)	1 (Years 0-5)	0	1 (Years 0-3)	1 (Years 0-3)
Off label use monitored/controlled	0	0	0	0	0
Monitoring of patient adherence	0	0	0	0	0
Enhanced safety monitoring	1 (begins Year 1)	1 (begins Year 1)	0	0	0
Adaptiveness Input Score	3	10	2	5	7

Summary of Significant **Outputs Factors** Adaptive Licensing Development Plans for Gilenya and Zelboraf

Input Factor / Attribute	Gilenya		Zelboraf (Orphan)		
Learning	**Actual**	**Adaptive Licensing**	**Traditional**	**Actual**	**Adaptive Licensing**
From passive surveillance	1	1	1	1	1
From prospective continuous learning	0	1	0	0	1
Regulator/Patient/Prescriber Metrics (appropriateness)					
Early access to some patients	0	1	0	1	1
Product used appropriately	Not modeled	Not modeled	Not modeled	Not modeled	Not modeled
Progressive reduction in uncertainty around safety and efficacy	0	1	0	0	1
Increased regulator confidence due to continuous learning over lifecycle	0	1	0	0	1
Enhanced medical and public confidence in safety and effectiveness of new medicines	0	1	0	1	1
Adaptiveness Output Score	1	6	1	3	6
Total Adaptiveness Score	4	16	3	8	13

Adaptive Pathways Can Increase OR Decrease Sponsor NPV

- Most cases increase sponsor NPV



Baird, Trusheim et al. Comparison of Stakeholder Metrics for Traditional and Adaptive Development and Licensing Approaches to Drug Development, *Therapeutic Innovation & Regulatory Science*, **47(4):**474-483 (May 2013).

Adaptive Pathways Potential for Patient

- Early patient access for effective therapeutics: Zelboraf
- Plus: reduced real exposure to risk: Gilenya
- Plus: Preserve access to appropriate patients even in the face of inappropriate excesses: Acomplia
- Plus: Increase ‘value for money’ by increasing appropriate use in real world populations

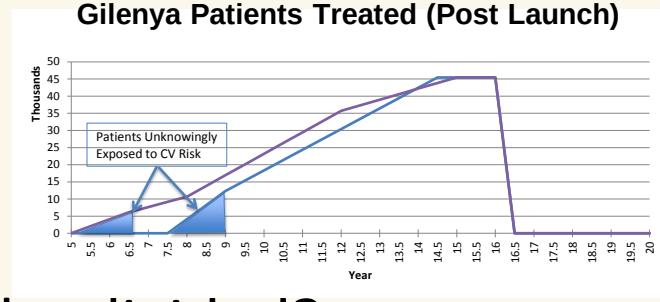
High Costs for Registry and Appropriate Access can Reduce Sponsor and System Sustainability

- System costs for surveillance, patient support and access control in the paper were set at $150-250/ patient per year
- For therapeutics valued at $20,000 to $40,000 or more per patient per year this proves affordable
- For therapeutics valued at $2,000 or less per patient per year, these costs substantially impact system sustainability

Sustainable Adaptive Licensing will benefit from, and may require, significant economies of scale for population surveillance, patient support and appropriate access control

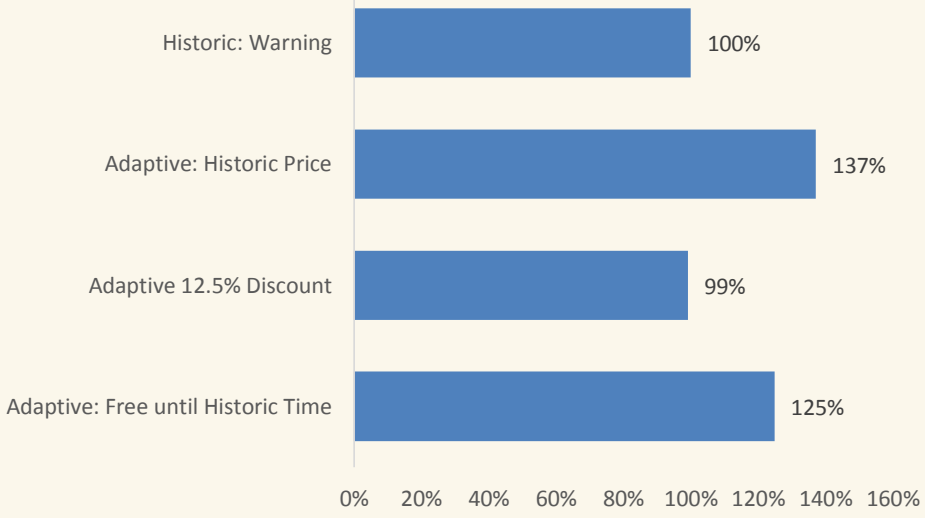
Evidence and Reimbursement: Room for Negotiation?

- Initial higher benefit population BUT less total experience
- Gilenya as example illustrates that classic development doesn't necessarily
- How might the early access advantages be divided?



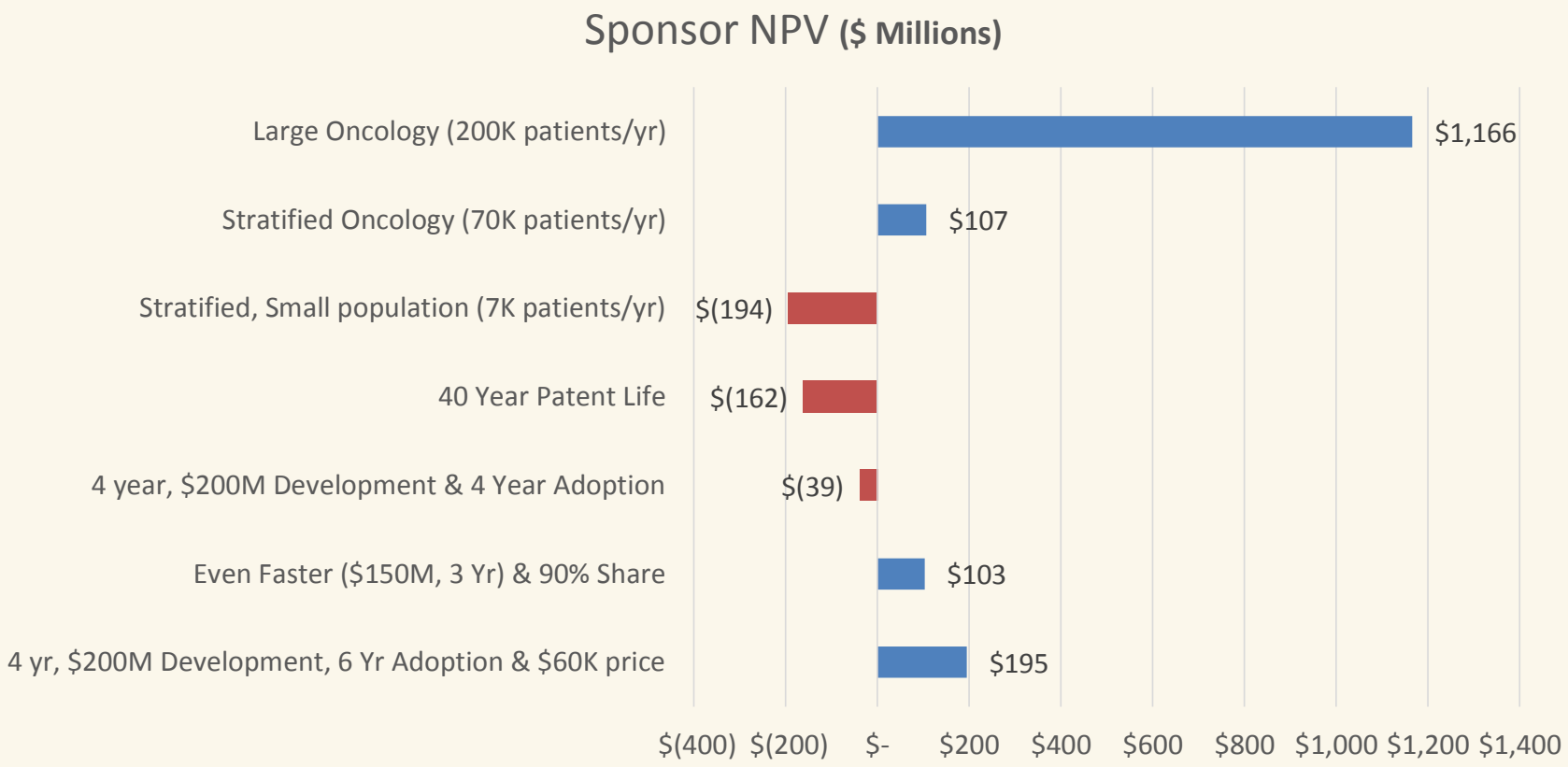
Specialty Product Alternative Reimbursement Approaches

(Based on Gilenya Case Study)



Common Disease "Orphanization" Needs New Approaches to Sustain Sponsors & Health Systems

- Scientific advances fragmenting diseases into small sub-populations
- Fast development mitigates financial challenges
- Adaptive licensing/reimbursement can provide a path



Trusheim, Berndt: Economic Challenges and Possible Policy Actions to Advance Stratified Medicine, *Personalized Medicine*, 9(4)413-427June 2012

NEWDIGS: Linking Thought Leadership to Action
Adaptive Licensing First Fruits

March 2012:
Multi-Stakeholder Thought Leadership

STATE OF THE ART

nature publishing group

Open

See COMMENTARY page 378

Adaptive Licensing: Taking the Next Step in the Evolution of Drug Approval

H-G Eichler[1,2], K Oye[2,3,4], LG Baird[2], E Abadie[5], J Brown[6], CL Drum[2], J Ferguson[7], S Garne
P Honig[10], M Hukkelhoven[11], JCW Lim[12], R Lim[13], MM Lumpkin[14], G Neil[15], B O'Rourke
D Shoda[18], V Seyfert-Margolis[14], EV Sigal[19], J Sobotka[20], D Tan[12], TF Unger[18] and G Hirsc

Traditional drug licensing approaches are based on binary decisions. At the moment of licensing, an expe
therapy is presumptively transformed into a fully vetted, safe, efficacious therapy. By contrast, adaptive li
approaches are based on stepwise learning under conditions of acknowledged uncertainty, with iterative
gathering and regulatory evaluation. This approach allows approval to align more closely with patient ne
access to new technologies and for data to inform medical decisions. The concept of AL embraces a range
Some see AL as an evolutionary step, extending elements that are now in place. Others envision a transfo
framework that may require legislative action before implementation. This article summarizes recent AL
discusses how proposals might be translated into practice, with illustrations in different therapeutic area
unresolved issues to inform decisions on the design and implementation of AL.

Clinical Pharmacology & Therapeutics (2012);
91 3, 426–437. doi:10.1038/clpt.2011.345

March 2014:
EMA Pilot Program

Home ▸ News and Events ▸ News and press release archive

European Medicines Agency launches adaptive licensing pilot project

Press release

19/03/2014

European Medicines Agency launches adaptive licensing pilot project

Improving timely access for patients to new medicines: pilot explores adaptive licensing approach with real medicines in development

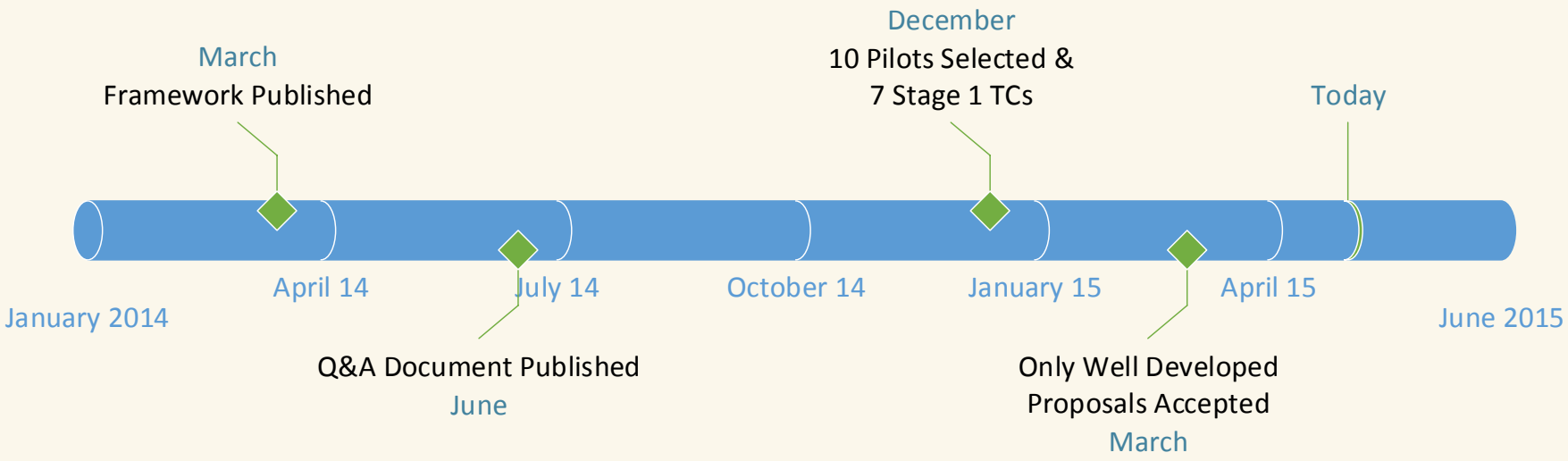
The European Medicines Agency (EMA) is inviting companies to participate in its adaptive licensing pilot project. Companies who are interested in participating in the pilot are requested to submit ongoing medicine development programmes for consideration as prospective pilot cases.

A framework to guide discussions of individual pilot studies has been published.

The adaptive licensing approach, sometimes called staggered approval or progressive licensing, is part of the Agency's efforts to improve timely access for patients to new medicines. It is a prospectively planned process, starting with the early authorisation of a medicine in a restricted patient population, followed by iterative phases of evidence gathering and adaptations of the marketing authorisation to expand access to the medicine to broader patient populations.

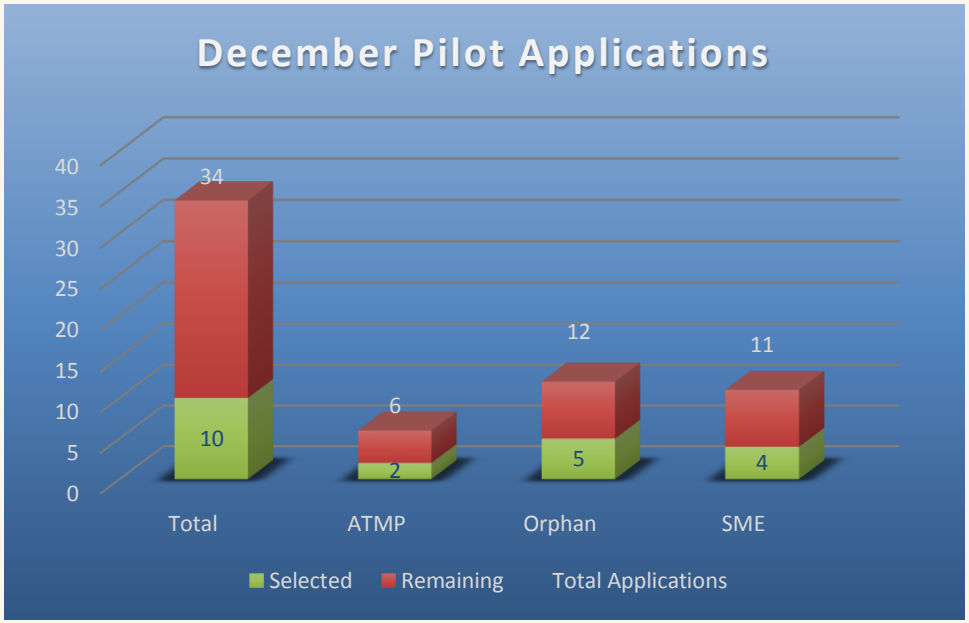
EMA Adaptive Licensing Pilots Status

- Name Changed to 'Adaptive Pathways' to
  - » "better reflect the idea of a life-span approach to bring new medicines to patients with clinical drug development, licensing, reimbursement, and utilisation in clinical practice, and monitoring viewed as a continuum."



Strong EMA Adaptive Pathway Application Flow

- December 2014:
  - » 34 applications received
  - » 10 Selected for Stage 1 Telecon
  - » 6 'well-designed submissions' selected for a safe harbor Stage 2 meeting:
    - 2-4 hour, in-depth discussions with all stakeholders
    - **Not** substitute for parallel SA/HTA advice
    - **Do not** focus on data and results
    - **Do** explore proposed plan and options for evidence development for SA, HTA, patient reported outcomes



EMA Adaptive Pathways Pilot Focus on Learning

- Iterative development plan with label extensions
- Use of real-world post-authorization data as a complement to RCT data
- Optimal use of regulatory tools
- Plan for HTA evidence development
- NOT classic Conditional Market Approval “fast track”

Adaptive Pathways and Basket Trials: A Perfect MATCH

NCI-MATCH Rationale

Molecularly targeted therapy has improved outcomes:

within individual tumor types:

- imatinib in CML (bcr-abl)
- imatinib in GIST (CKIT & PDGFRα)
- erlotinib in NSCLC (EGFR)
- crizotinib in NSCLC (EML4-ALK)

and, across tumor types:

- trastuzumab in breast & gastric (Her-2)
- vemurafenib in melanoma, thyroid & NSCLC, but not colon cancer (BRAF)

NCI-MATCH Hypotheses

Primary:

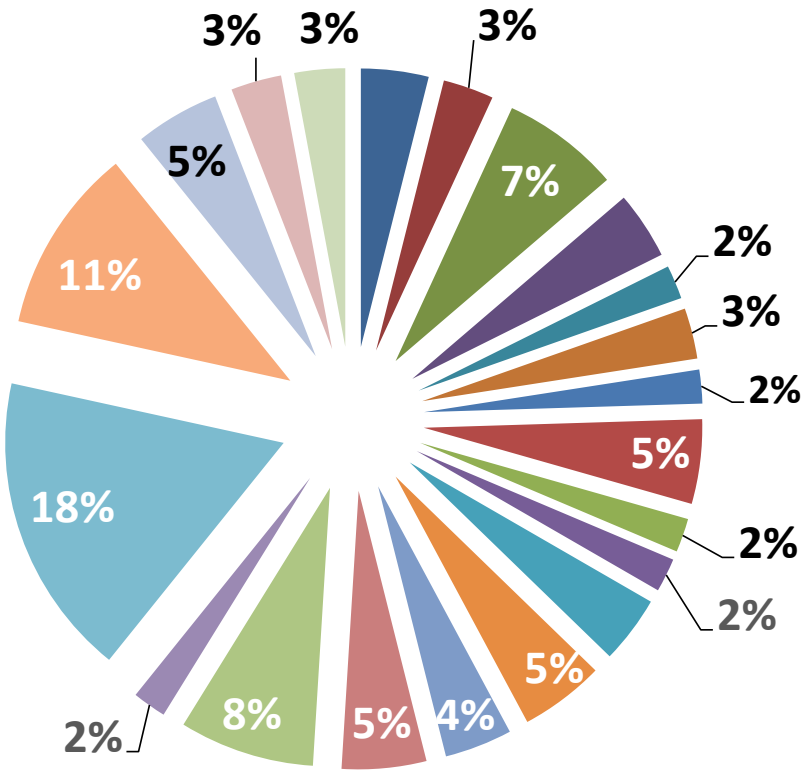
Tumors that share common somatic genetic alterations in oncogenes will be variably responsive to therapies targeting the oncogenic pathway based on lineage specific factors.

Secondary:

Concomitant somatic genetic alterations will predict responsiveness or resistance.

aMOIs in NCI MATCH and Estimated Prevalence

aMOIs (actionable mutations of interest):



- ALK translocations - (4%)
- BRAF fusions or non-V600E, non-V600K mutations - (2.79%)
- BRAF V600E or V600K - (1-12%)
- cKIT mutations - (4%)
- DDR2 mutations - (2%)
- EGFR activating mutations - (1-4%)
- EGFR T790M mutations - (1-2%)
- FGFR amplifications or FGFR mutations - (5%)

MATCH Creating Efficiencies and More Comparable Evidence

- MATCH Phase Ib US national network already is:
  - Standardizing outcome metrics
  - Examining multiple new candidates
  - Using shared standard of care arm(s) with 'candidates' becoming tomorrow's comparators
  - Gaining efficiencies in trial approvals, site training, recruitment, etc.
  - Seeking to retire separate clinical trial systems and simply upgrade the medical EHR to clinical trial quality standards

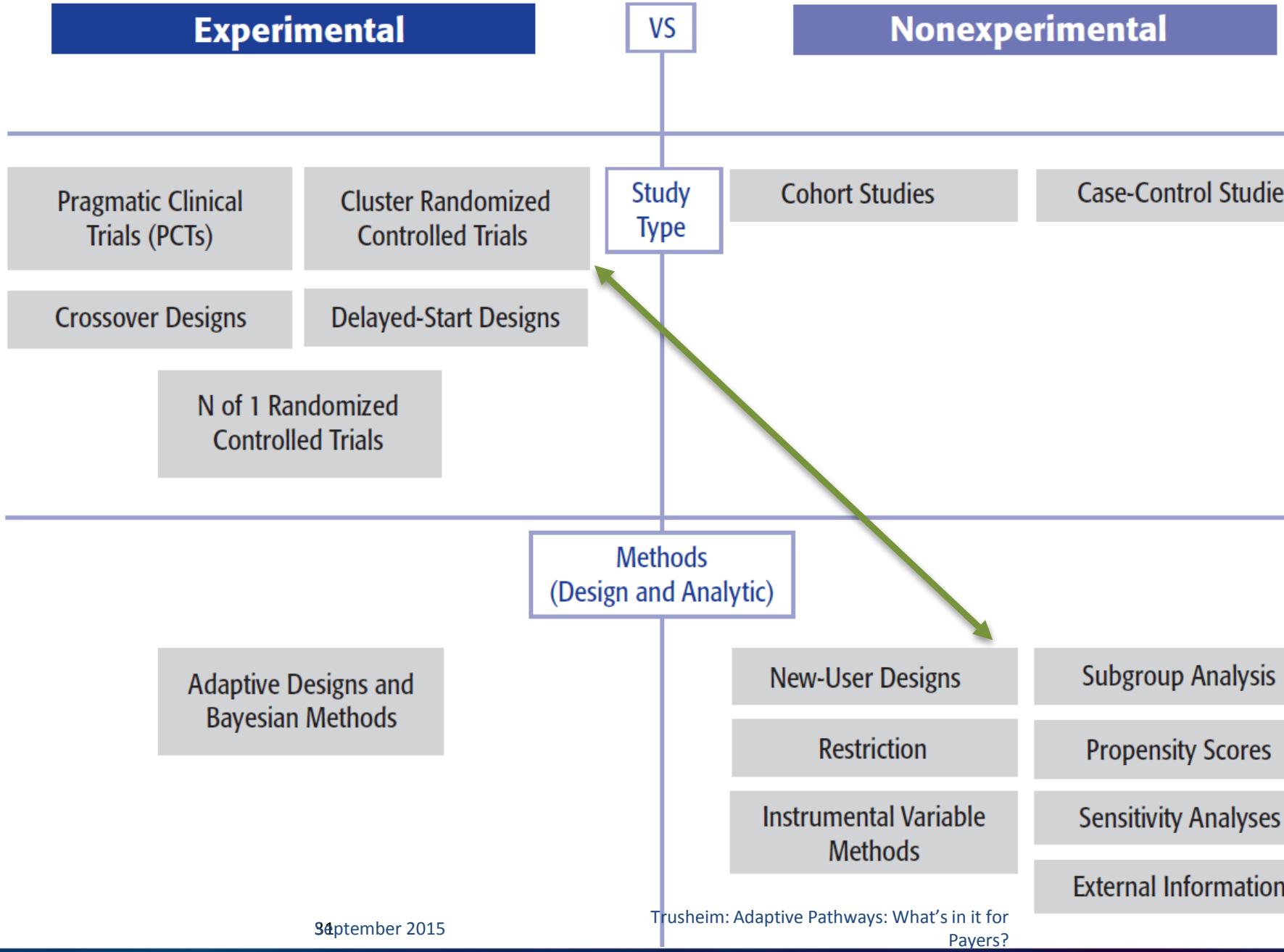
Extending MATCH to Pivotal Trials & Beyond

- Imagine extending these designs and operating principles forward into pivotal trials (each sponsor paying for their candidates' arms) to generate broader, comparable clinical efficacy and effectiveness evidence.
- Then, since it is leveraging the medical practice EHR system, continue forward into a more observational post-approval/REMS setting to replace registries and implement Phase IV trials
- Advantages
  - Sponsors: Superior products will be clearly demonstrated with faster up-take
  - Payers: Comparable, evolving and updated clinical utility evidence for access and reimbursement
  - Creative reimbursement approaches may be enabled if tracking/admin burdens reduced
  - Patients: Clearer, faster access to best personalized care-whether approved or investigational therapies
  - Regulators: Clearer, cleaner submissions for evaluation

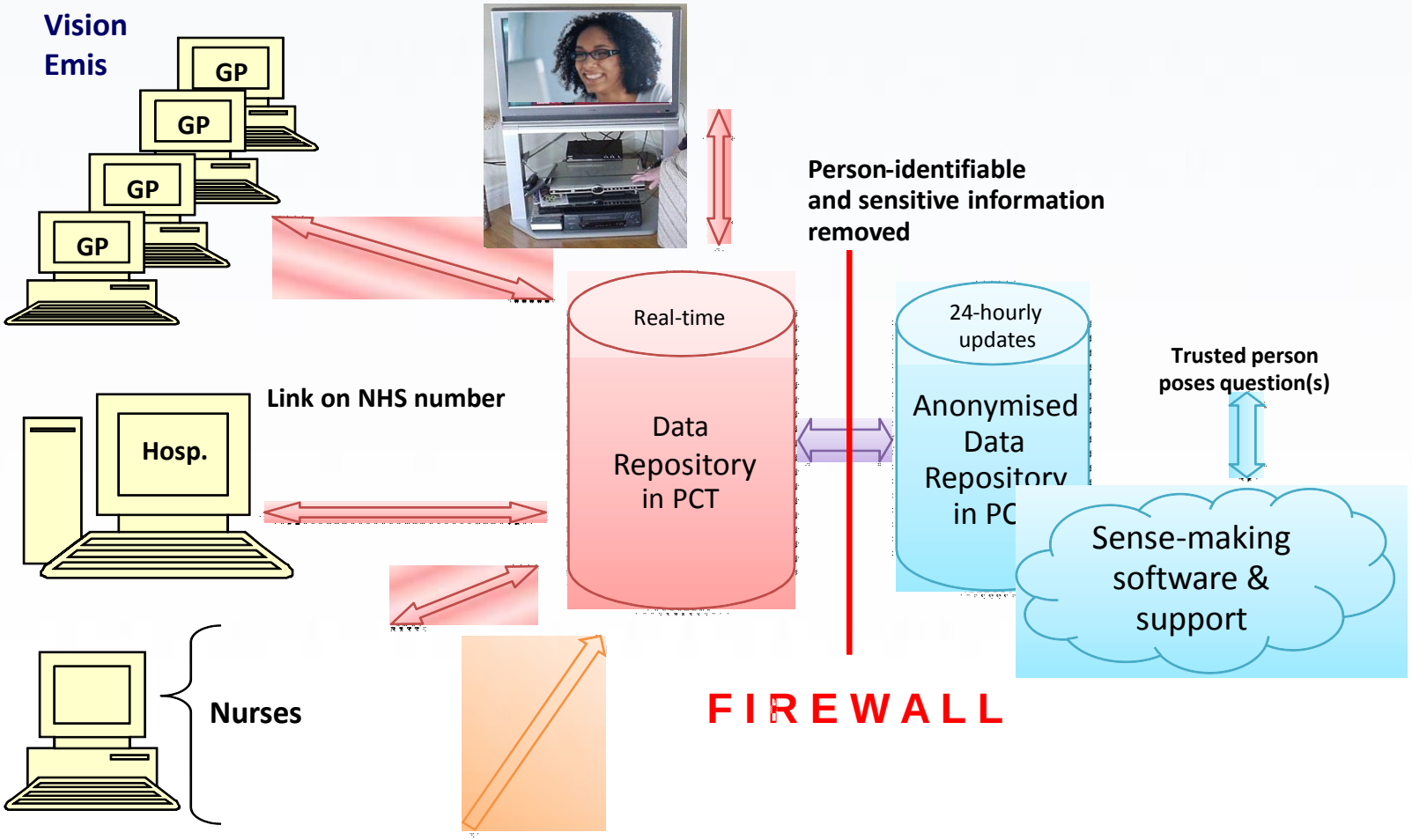
Real World Evidence: types, uses and concerns

How will the new Adaptive Pathways leverage "real world" big data to achieve their potential?

Figure 1. Experimental and nonexperimental study types and methods



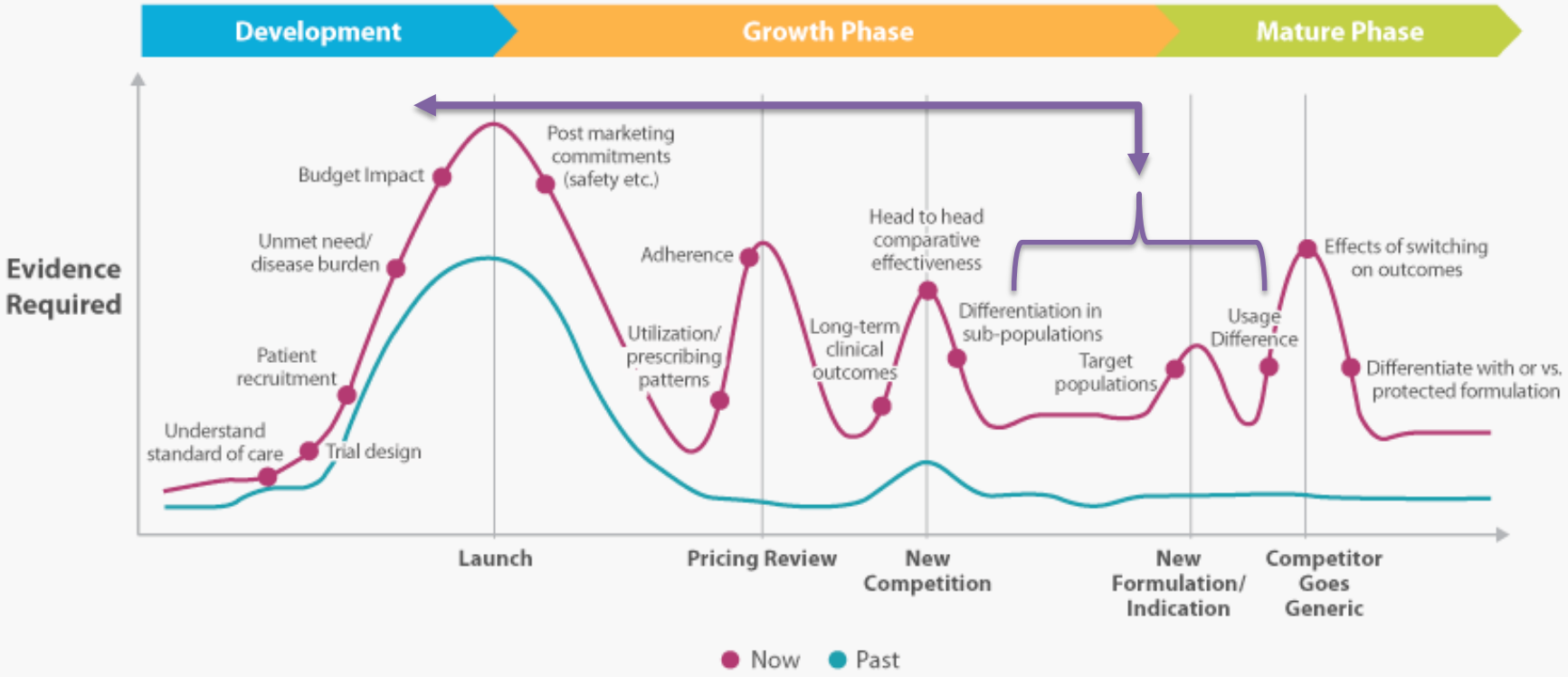
Linked Primary & Secondary Care Data Sources



Demographics, Patient reporting

The research leading to these results has received support from the Innovative Medicines Initiative Joint Undertaking under grant agreement no [115303], resources of which are composed of financial contribution from the European Union's Seventh Framework Programme (FP7/2007-2013) and EFPIA companies' in kind contribution.
www.imi.europa.eu

RWE Intensifying Across Product Lifecycle



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Sources of Sub-Population and Usage Data Outside the Project Studies

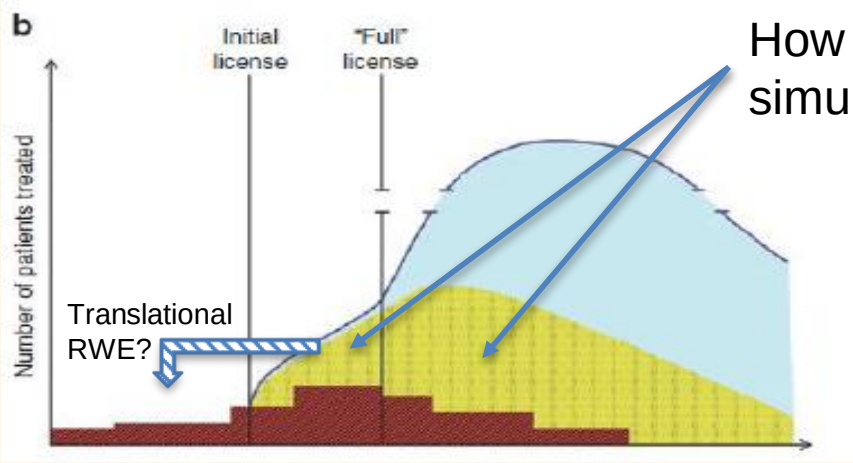
- Biobanks
- Natural History of Disease studies and databases
- Patient Registries
- EHR data to inform the above

Significant opportunity for Payers to
Inform and influence product goals & development

Adaptive Pathways Anticipate Pre-Planned, Life Span Evidence Generation

- If RCT propensity scoring/generalizability is anticipated
  - » What RWE can be collected PRIOR to pivotal RCT initiation to improve RCT design for later propensity extrapolation?
  - » What RWE could be collected during RCT to refine extrapolations and patient access?
- What RWE should be collected during early launch to test & refine the license and access?
- Increasingly we are moving towards stratified or precision medicine which harnesses variability. How can payers, regulators and developers harness variability through adaptive licensing and not simply be slaves to the mean at time of initial approval?

Adaptive Pathways



How to optimally, adaptively design this simultaneous RCT & RWE collection?

MIT CBI, Eichler et al (Mar 2012) CP&T 91(3)426:437

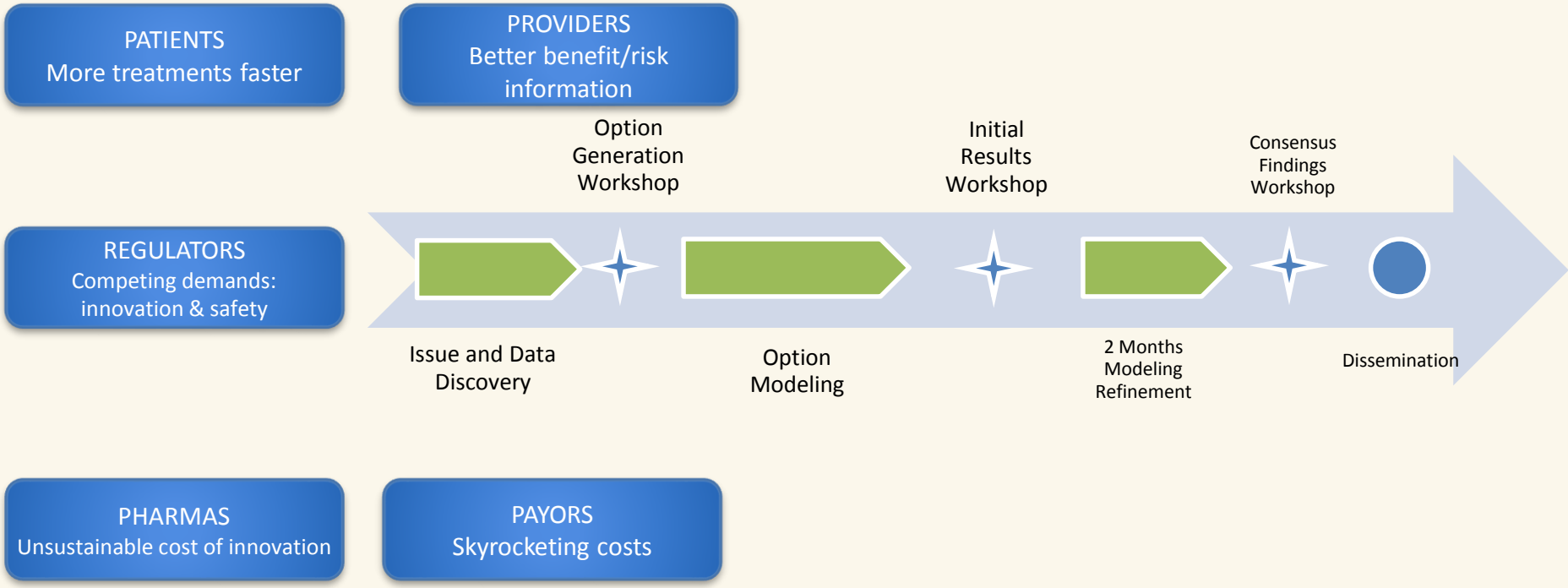
Janus Program:
Combining Perspectives in a Quantitative Process

New Pathways Challenge Analytical Frameworks

- New Pathways Connect formerly independent stages
  - » Scientific discoveries target new sub-populations which define indications, patient access and markets
  - » One trial asked to answer many questions: safety, efficacy, variability, sub-populations & diagnostics, clinical utility
  - » Earlier patient access blurs experimental versus approved treatments for payers
  - » Real world data augments, even substitutes, for randomized clinical trials: especially for safety evidence
- New connectedness requires connected designs, processes and analytical tools

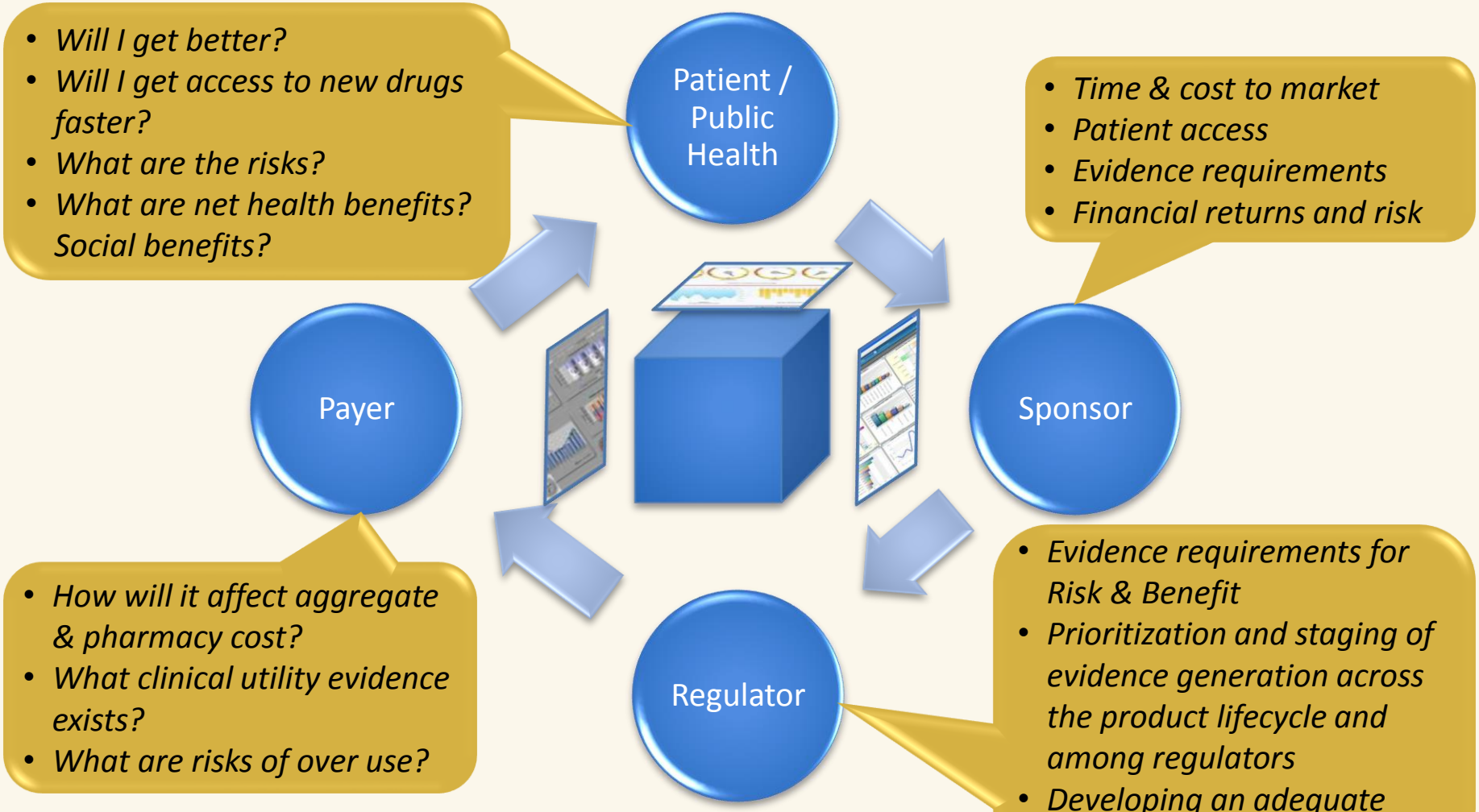
Satisficing All: The Janus Program

- Each stakeholder has a veto, so all must agree
- Beyond the Spirit of agreement, can the numbers work?
- Multi-Stakeholder Process and impact Quantification



Janus Program – Helping Stakeholders Move from Lists to Balanced Alternatives

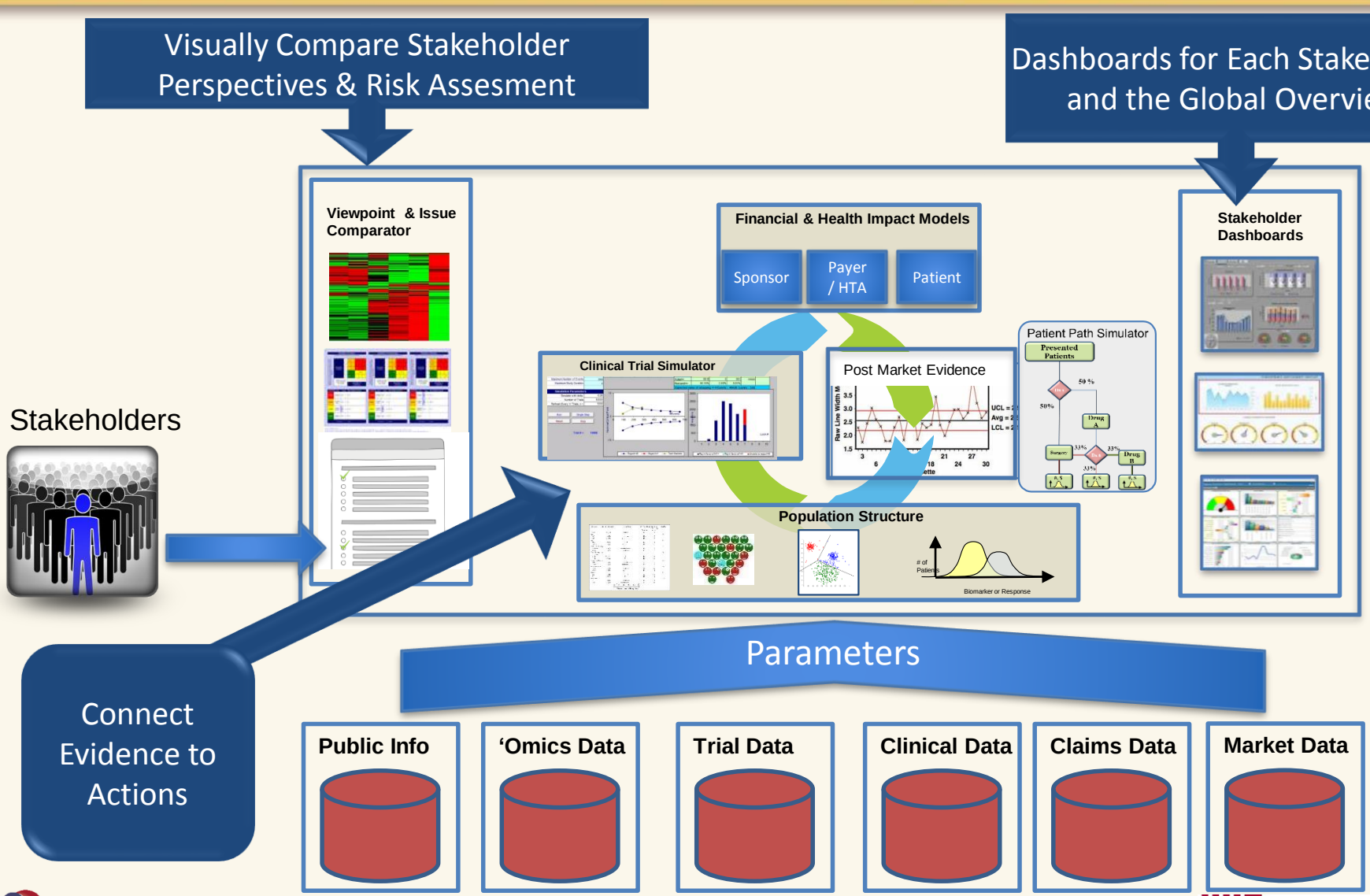
Single Process to Explore Therapeutic Impact for all Stakeholders



Janus Program: Leveraging Bioinformatics to Discover Stakeholder Perspectives and Structure Discussion

- Viewpoint, Issue & Input Evidence Comparator
  - » Quickly highlights main areas of concern
  - » Shows relative perspective concordance

Janus Program:
Quantified, Connected Stories to Develop Creative Consensus



Janus Program: More than a Process Informed by Models – A Forum for Collaborative Solution Creation

- Study/model the effect of changes in the access of health technologies
  - On patients
  - On health care budgets
  - On health care providers
  - On clinicians
- Building towards interactive 'war gaming'
- Can help assess data types, quality and designs needed to monitor/evaluate the changes
- May provide a realistic picture of the effects of our joint actions
- Beginning pilots now
- We welcome your ideas and participation

Adaptive Pathways: Patient First But No One Last

- Patients: Early, appropriate access refined over time and accounting for their preferences
- Regulators: Staged benefit / risk improving over time
- Payers: Deliver better health while stewarding resources
- Providers: More therapeutic options with improving knowledge of which are best for whom
- Sponsors: Sustainable innovation chain from science to patient to investor

Success Requires Increased Collaboration Supported by Prospectively Planned Evidence & Decisions to Build Trust and Viability

Thank You!

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24 September, 2015
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