Better Science, Better Health

New Pathways & New Sources of Evidence, what do we need?

21 October 2014

MAPPs and Adaptive Licensing: Connected Evidence Development, Shared Stakeholder Impacts

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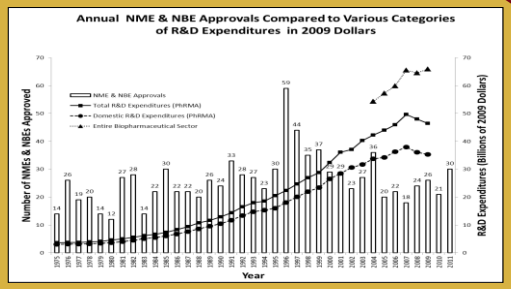
NEWDIGS: A Systems Approach to Enhancing the Value & Sustainability of Pharma Innovation

PATIENTS
More treatments faster

"We simply don't have time to wait for the results [of clinical trials]. Our life spans are shorter than the [regulatory] approval process."

"Frustrated ALS Patients Concoct Their Own Drug," Wall Street Journal, April 15, 2012

PHARMAS
Unsustainable cost of innovation



Burrill & Co. Analysis for PhRMA 2006-2011

NEWDIGS Mission: Reliably & sustainably deliver new, better, affordable therapeutics to the right patients faster.

PROVIDERS
Need better benefit/risk information

"I rarely prescribe a new drug during the first 2 years it has been on the market. There is too much uncertainty about safety during this time."

Neurologist, Boston

REGULATORS
Competing demands: innovation & safety

"Our current regulatory model sets unrealistic expectations for the public that it is possible to eliminate all uncertainty about product safety prior to market approval."

Senior Official, FDA

PAYORS
Skyrocketing costs

"If companies want premium pricing for their drugs, they need to demonstrate premium value."

John LaMattina, PureTech Ventures

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.

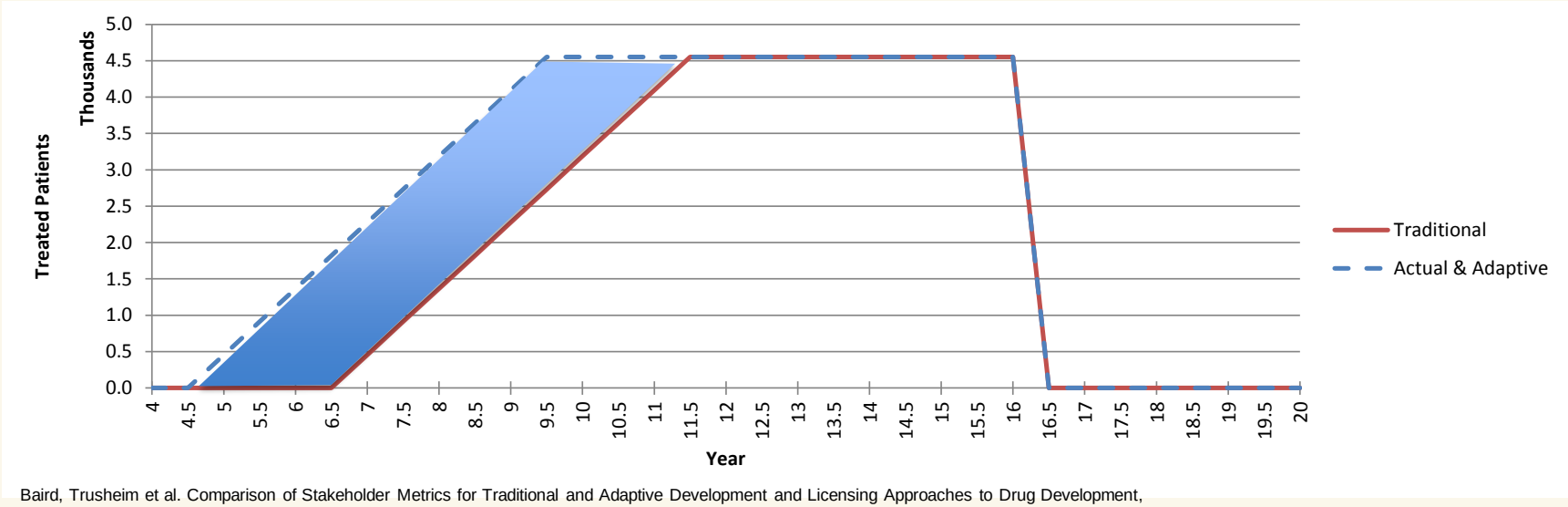
A framework to guide discussions of individual pilot studies has been published.

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.

MAPPs/AL Can Increase Patient Access: Zelboraf

- Vemurafenib: BRAF inhibitor for metastatic melanoma approved on Ph 2 & halted Ph 3 data.
- **9,100 additional patient treatment years** (40% eligible patients treated at peak)
- 66% NPV, 47% eNPV increase for sponsor in Actual due to
  - » earlier time to market: only 4.5 years
  - » reduced development costs: 164 Ph 1/ 2 patients and 675 in halted Ph 3
  - » extended period of peak sales

Zelboraf Patients Treated (Post Launch)



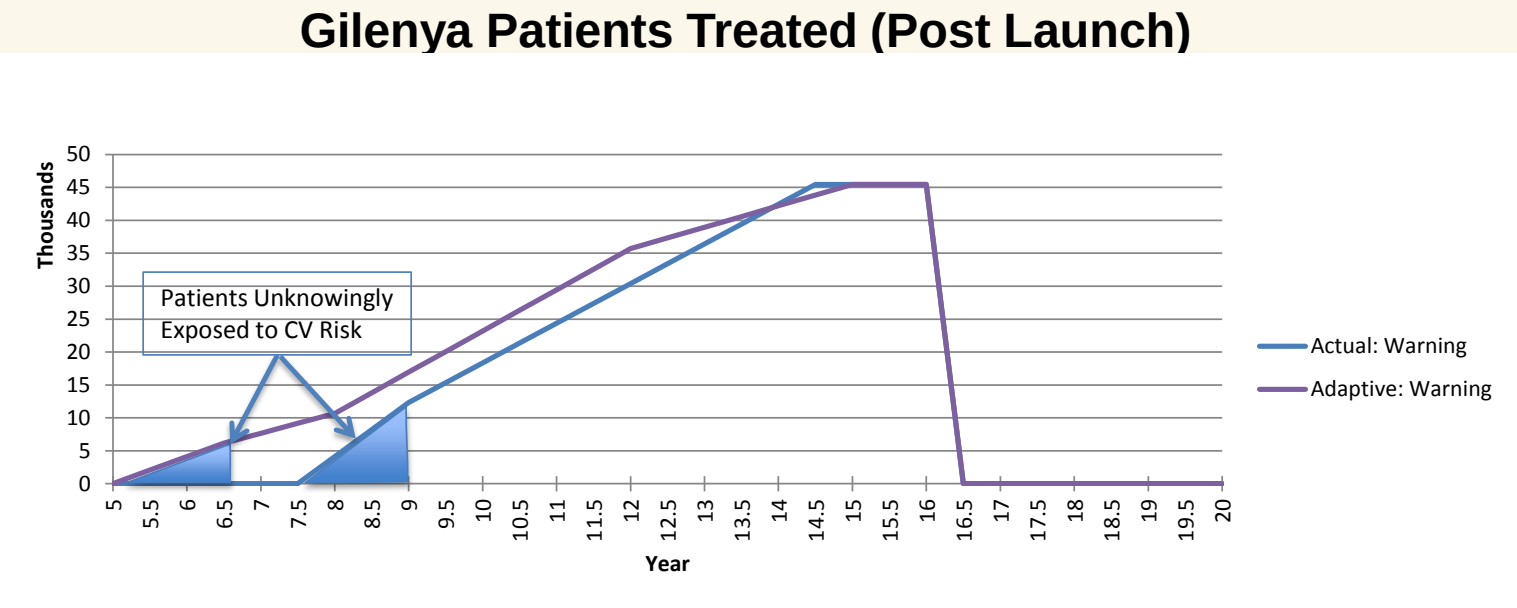
Baird, Trusheim et al. Comparison of Stakeholder Metrics for Traditional and Adaptive Development and Licensing Approaches to Drug Development, *Therapeutic Innovation & Regulatory Science*, **47(4):**474-483 (May 2013).

Gilenya Scenario Summary

- Fingolimod: Multiple Sclerosis oral agent. Immunomodulator thought to act via S1PR1 receptor(s).
- Classic:
  - One Approval: Treatment of patients with relapsing forms of MS to reduce the frequency of clinical exacerbations and to delay the accumulation of physical disability
- MAPPs/AL Scenario:
  - Indication at first approval: Treatment of patients with moderate to severe relapsing MS to reduce the frequency of clinical exacerbations and to delay the accumulation of physical disability. Patients must be treated under close supervision and be enrolled in a registry.
  - Indication at second approval: Treatment of patients with relapsing MS to reduce the frequency of clinical exacerbations and to delay the accumulation of physical disability.

MAPPs/AL Can Reduce Patient Realized Risk

- Post-launch discovery of safety concerns partially due to REMS at time of approval
- Approach may have reduced patients exposed at higher risk (8K patient exposure years versus 16K)
- Also could improve sponsor economics



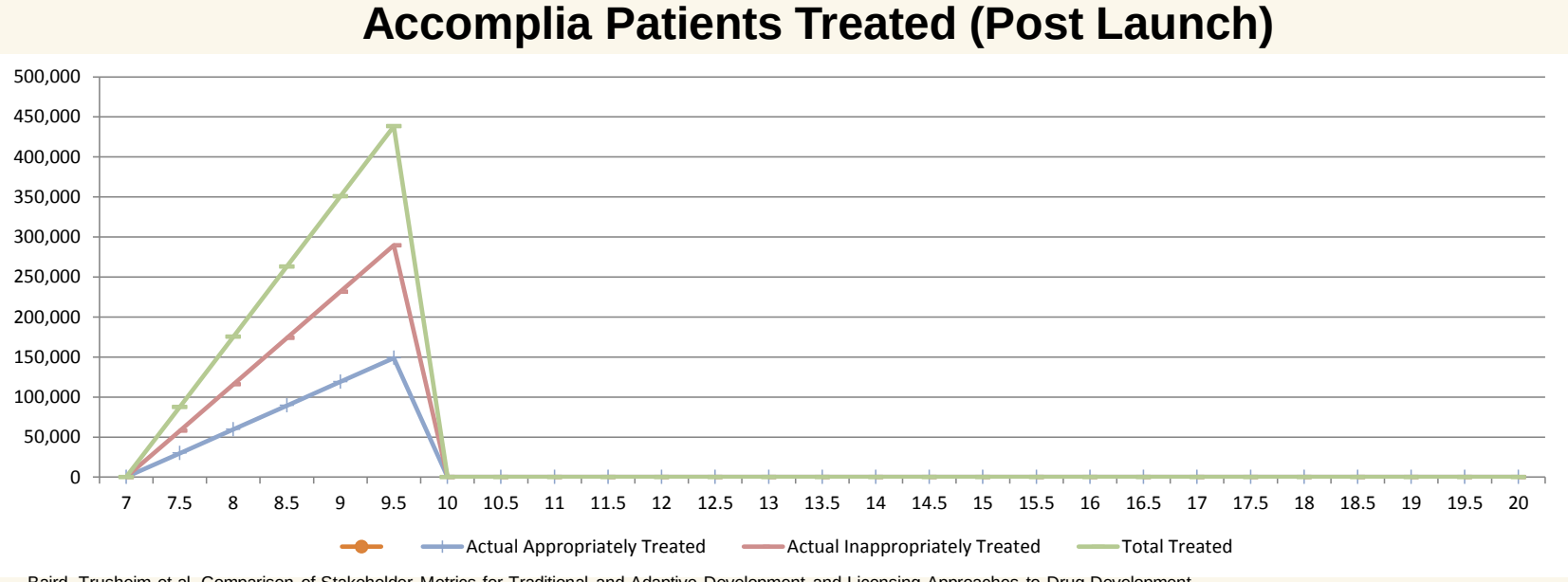
Baird, Trusheim et al. Comparison of Stakeholder Metrics for Traditional and Adaptive Development and Licensing Approaches to Drug Development, *Therapeutic Innovation & Regulatory Science,* **47(4):**474-483 *(*May 2013).

Acomplia Overview

- Acomplia (rimonabat) is a selective antagonist of the cannabinoid type 1 receptor developed as an anorectic anti-obesity treatment for those with additional risk factors (T2 diabetes or dyslipidemia)
- Approved in EU in 2006. Not approved in US
- Warnings regarding psychiatric side effects, particularly depression, in original EU label and strengthened in 2007
- Due to psychological side effects including suicidality, Acomplia was withdrawn in 2009

Acomplia: Historical Experience

- Approved by EMA, not in US
- Significant clinical use with high rates of use in those with psychiatric issues or otherwise inappropriate
- Product withdrawn in EU after 3 years due to safety issues in inappropriately treated patients



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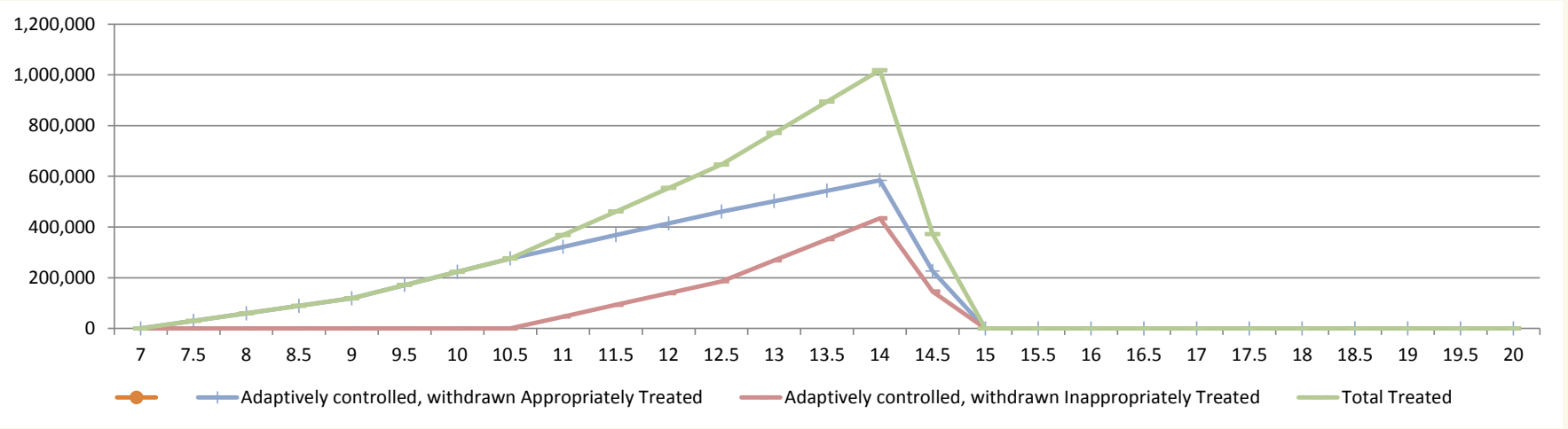
Acomplia: Iterative, Titrated MAPPs/AL

- Actual development program with strict controls after approval, US lags
- Review after ~3 years, support and controls removed, registry remains
- Sponsor pays for support, controls and registry

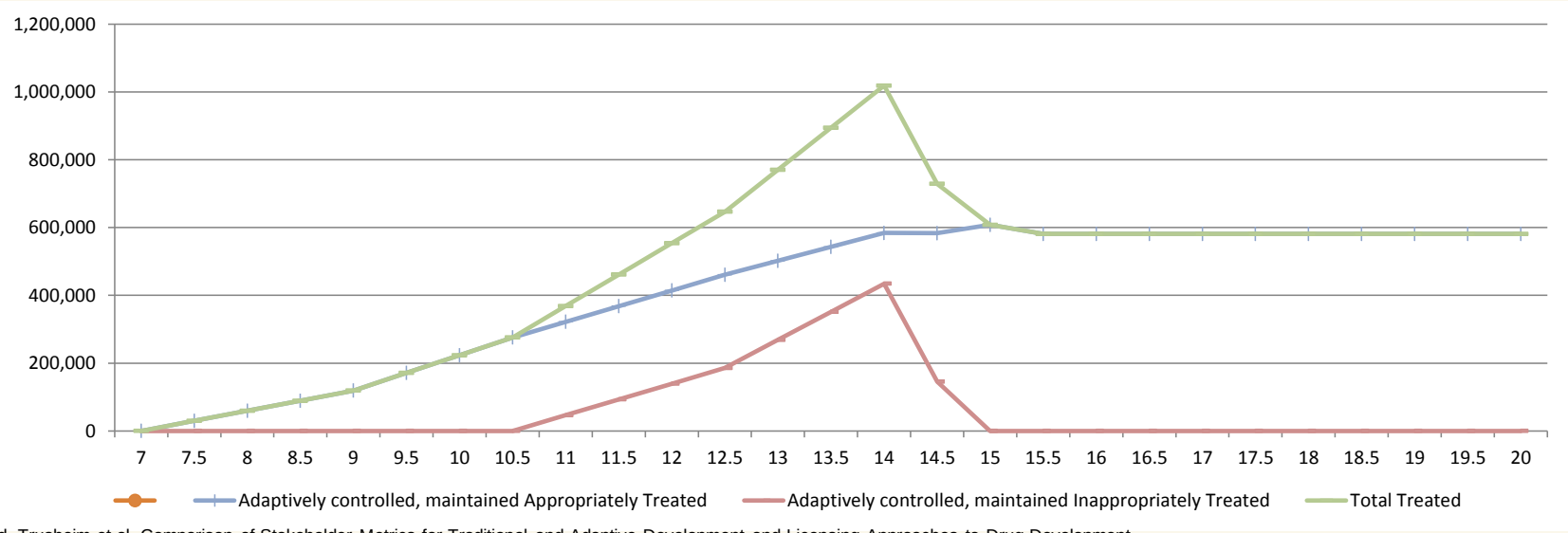
Acomplia:
Adaptively Controlled, Relaxed Unsuccessfully and Withdrawn

- Initially highly controlled,
- Controls relaxed after 3 year review
- Explosion of inappropriate use leads to withdrawal at 6 year review



Acomplia:
Adaptively Controlled, Relaxed Unsuccessfully and Recontrolled

- Same as previous scenario, but controls reimposed rather than withdraw
- Patients inappropriately treated halted, but access retained



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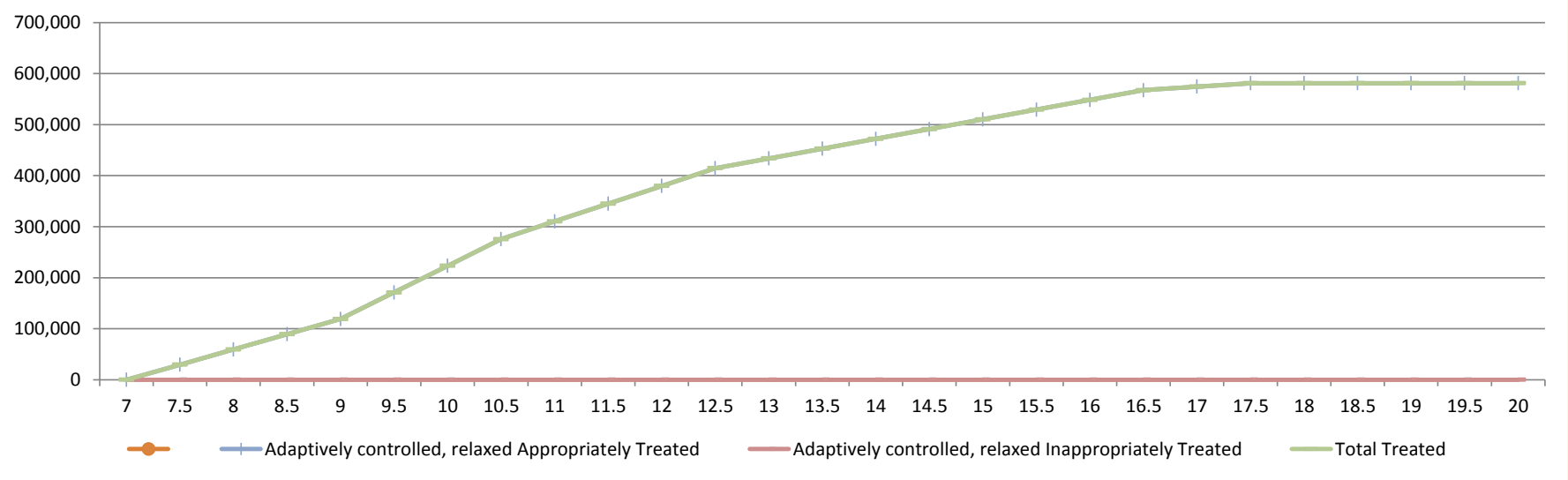
Acomplia:
Adaptively Controlled, Relaxed Successfully After 3 Years

- Initially highly controlled,
- Controls relaxed after 3 year review
- Success of provider, patient training and sponsor enlightened self-interest leads to continued appropriate use
- US approval 2 years after EMA approval

Acomplia Patients Treated (Adaptively Controlled, Relaxed)



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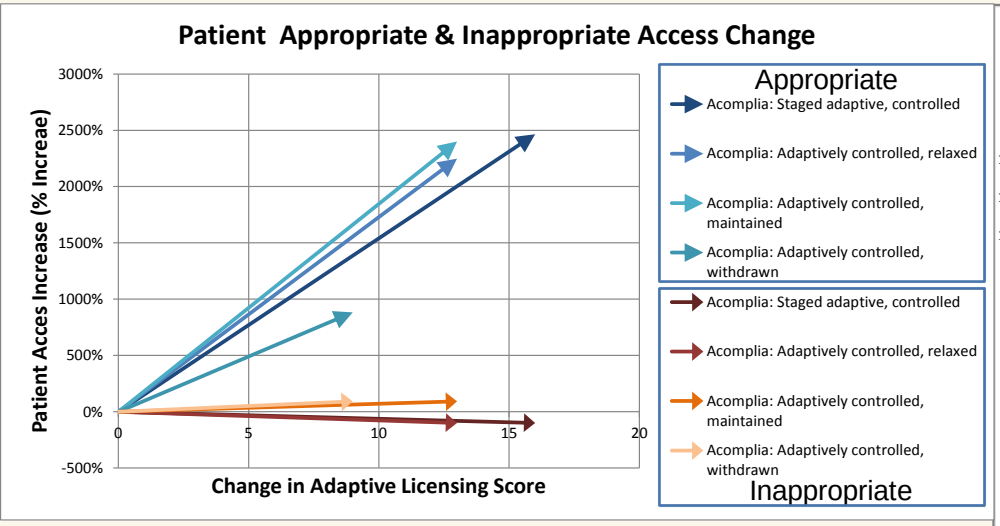
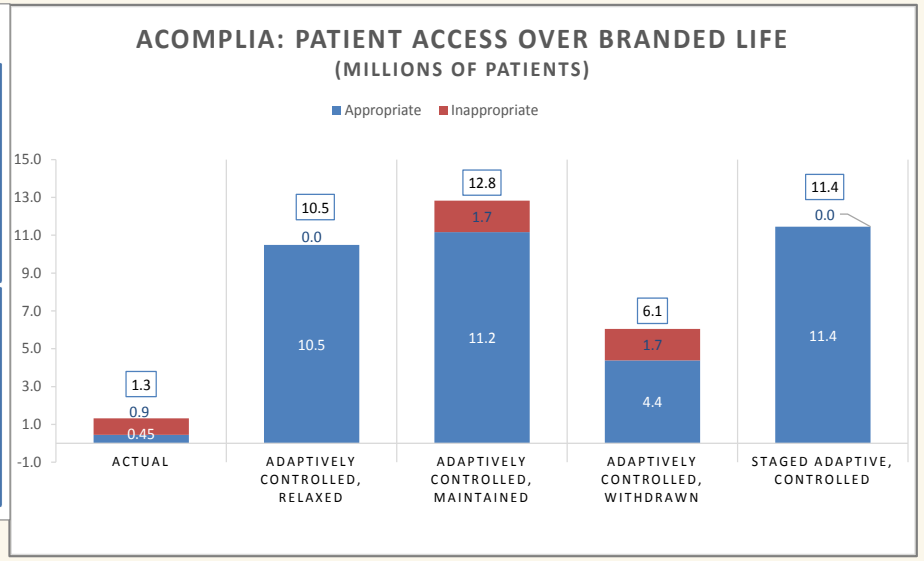
Larger AL Scores Tend Towards Improved Patient Access

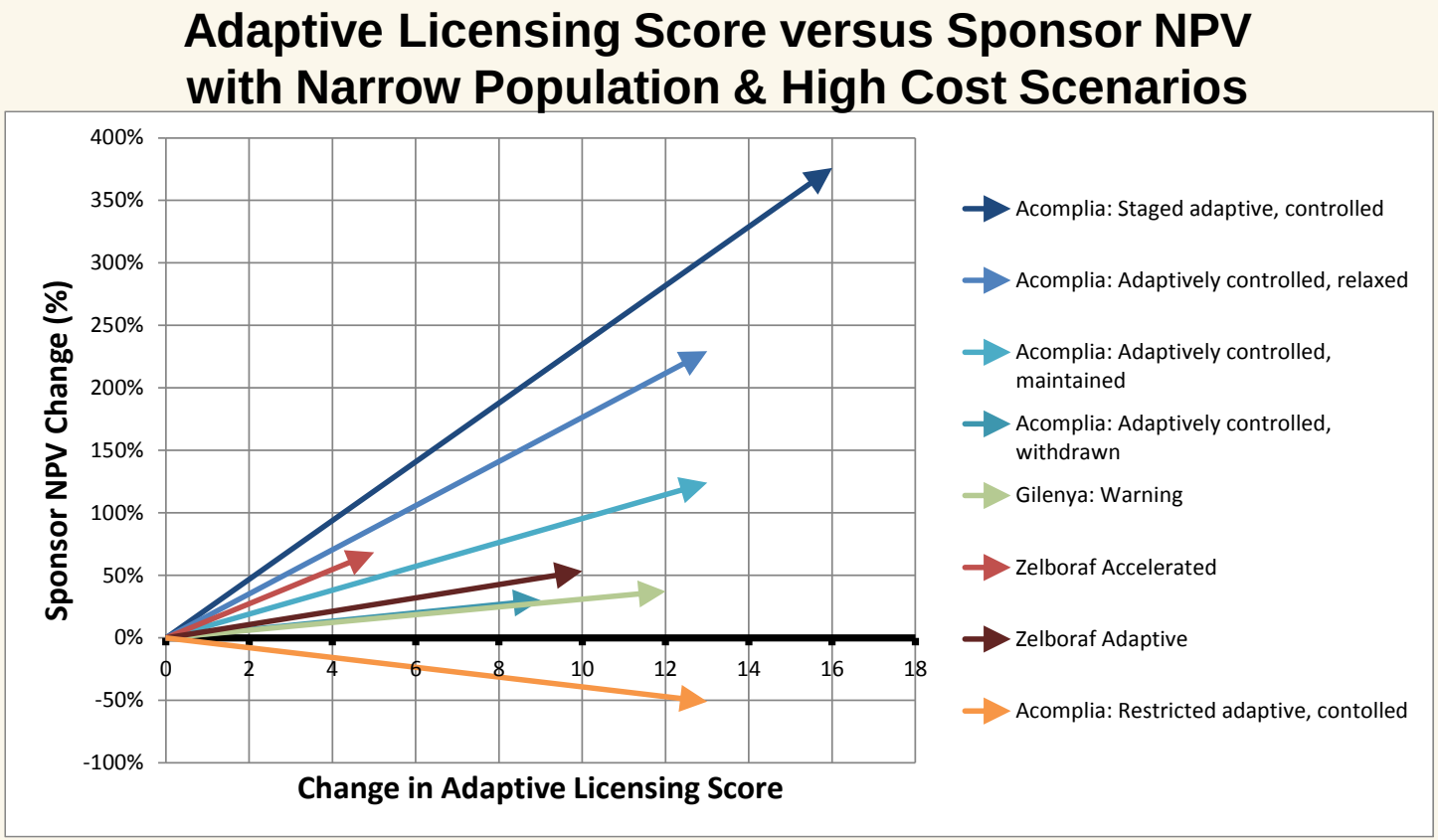
- Acomplia example
  - » More patients receive access
  - » A higher fraction receive appropriate access
  - » Requires effective, efficient clinical support & monitoring





MAPPs/AL Can Increase OR Decrease Sponsor NPV

- Most cases increase sponsor NPV



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MAPPs/AL 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

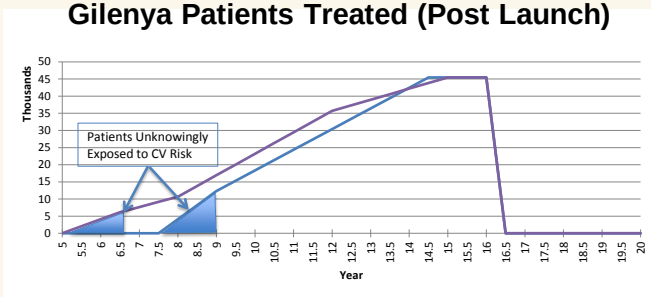
High Costs for Registry and Appropriate Access can Reduce Sponsor and System Sustainability

- 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

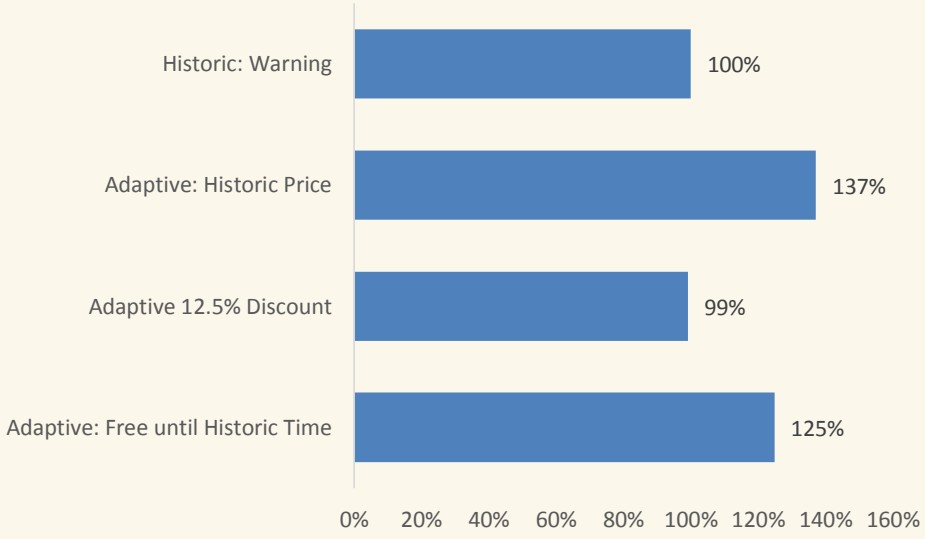
Sustainable Adaptive Licensing will benefit from, and may require, significant economies of scale for population surveillance, patient support and appropriate access control

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?

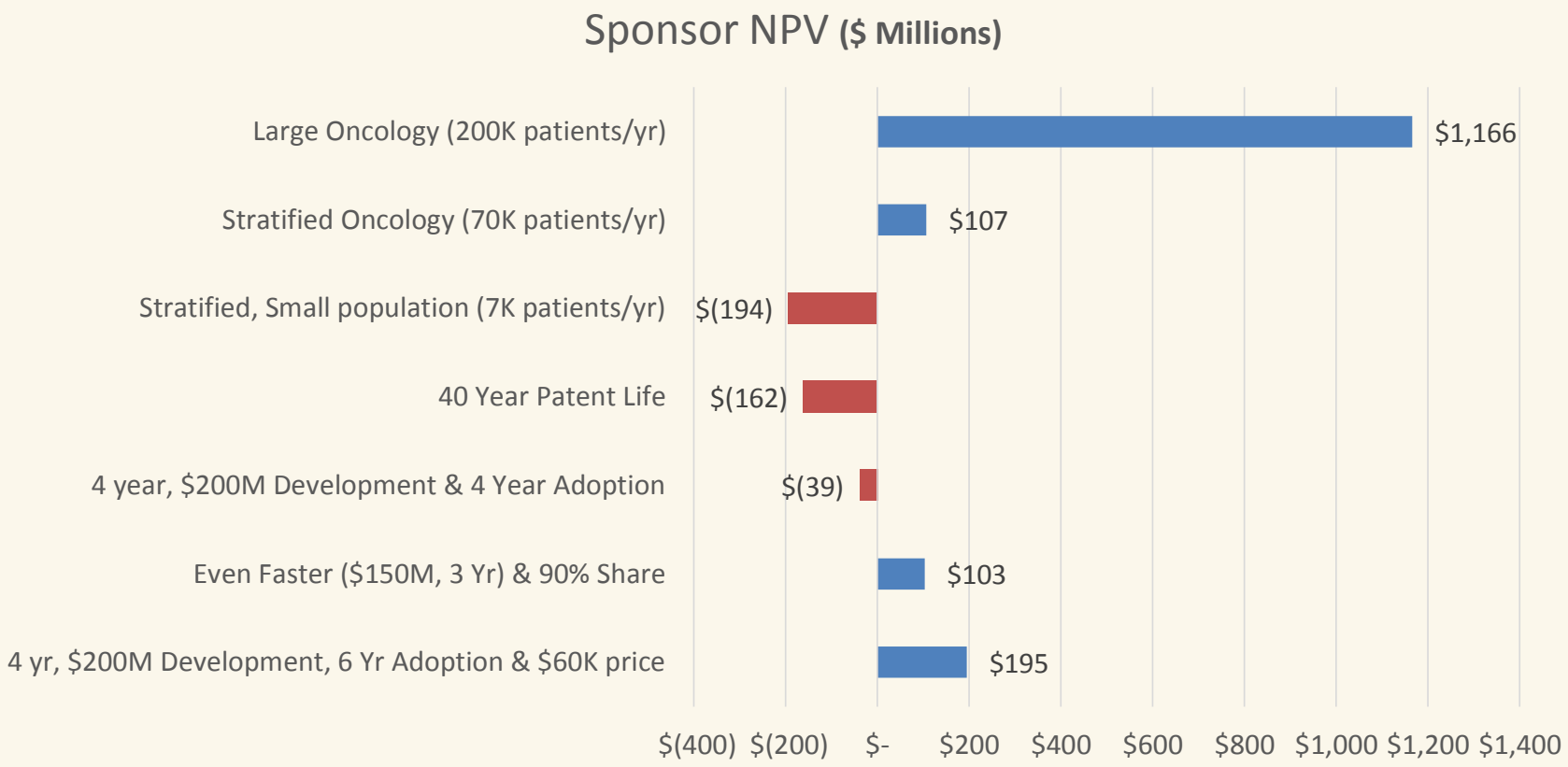


Specialty Product Alternative Reimbursement Approaches
(Based on Gilenya Case Study)



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



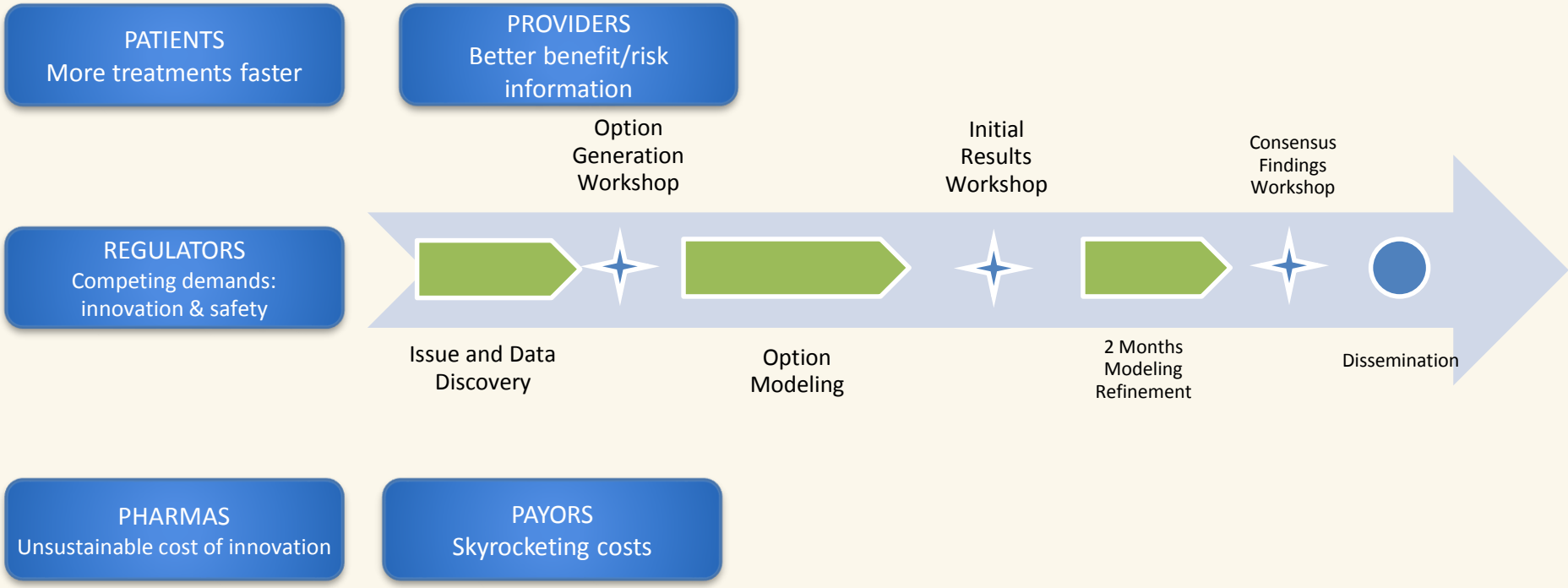
Trusheim, Berndt: Economic Challenges and Possible Policy Actions to Advance Stratified Medicine, *Personalized Medicine*, 9(4)413-427June 2012

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 Initiative

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



Adaptive Licensing: New Approach, New Evidence

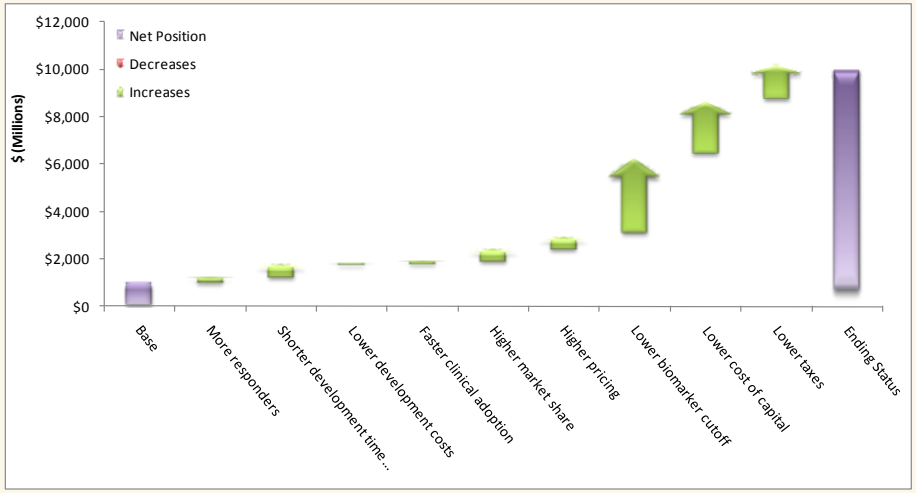
- Evolving license over therapeutic life span
- Clinical Trial: adaptive to basket to N of 1
- Real World Data 'fit for purpose' for policy decisions
- Patient population variability understood and tied to clinical population outcomes
- Patient preferences explicitly accommodated

Success Requires Increased Collaboration Supported by Prospectively Planned Evidence & Decisions

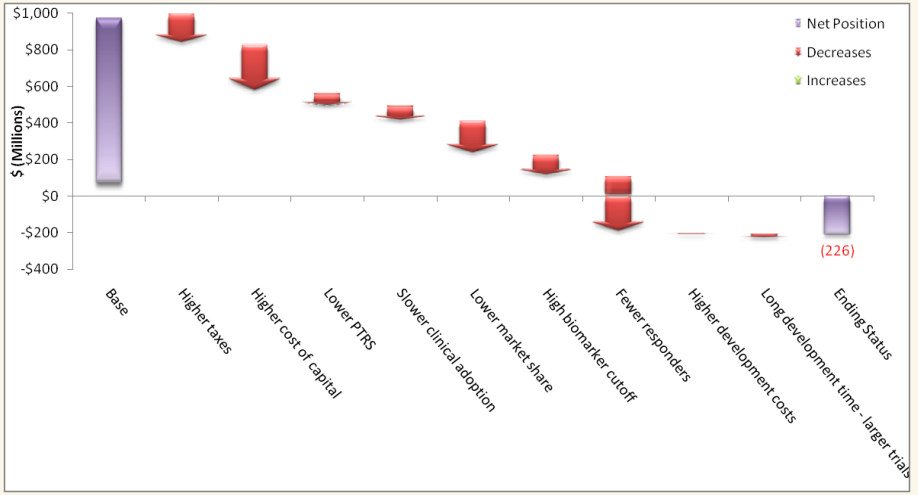
Alternative Future Worlds
Compounding Connections Yield Dramatic Endings

- In Stratified (Personalized) Medicine development, the factors are not just additive, but multiplicative
- $1B NPV stratified medicine example
- 9 factors +/- 25% from development time to clinical adoption speed to market share

Nirvana



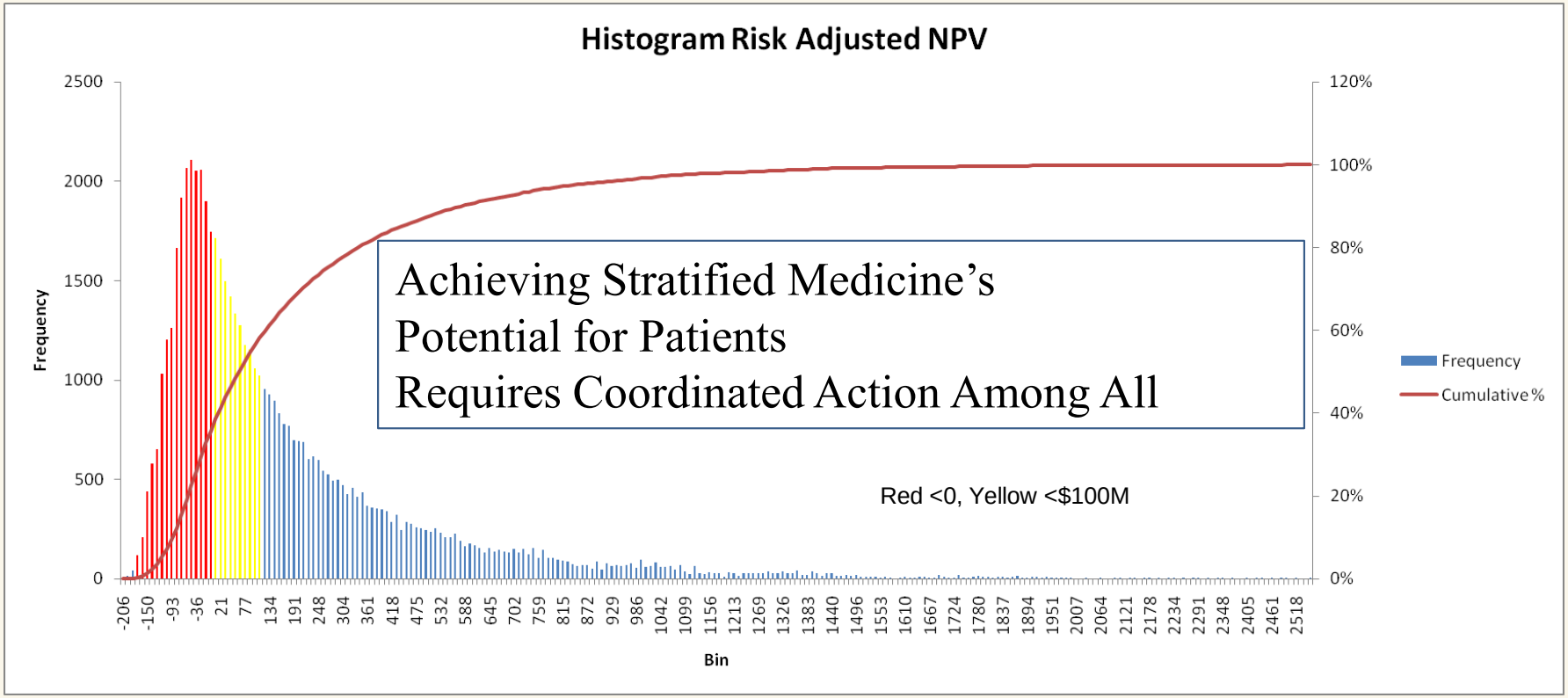
Pharmageddon



Trusheim et al. Quantifying factors for the success of stratified medicine. Nature Reviews Drug Discovery 10, 817-833 (Nov 2011)

More Poor Futures than Rich Futures

- >500,000 potential futures exist by combining 12 factors
- 36% of cases are negative risk adjusted NPV, 21 % 0<x<$100M and only 3%>$1B (not including tax rate and cost of capital cases)

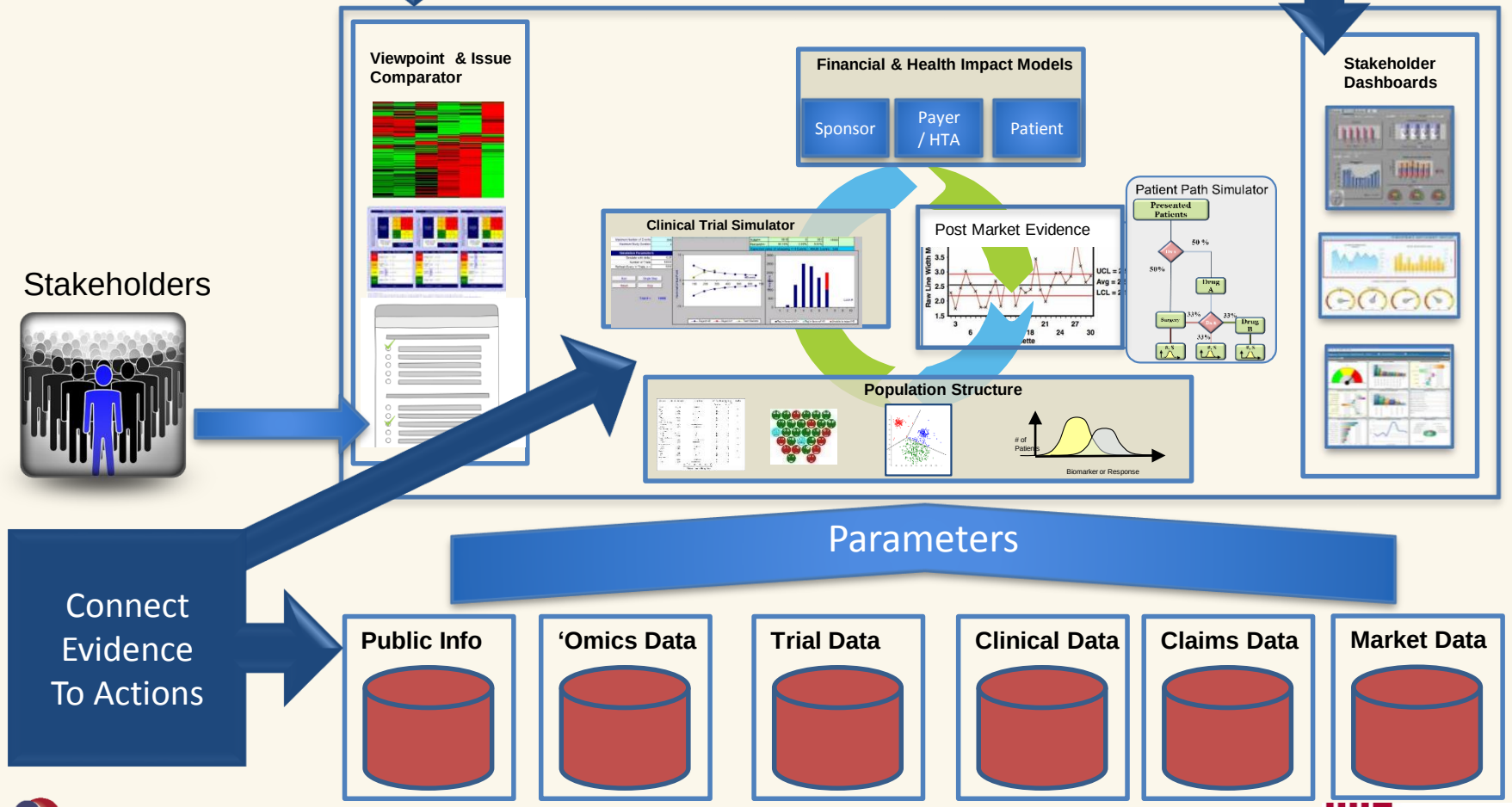


Trusheim et al. Quantifying factors for the success of stratified medicine. Nature Reviews Drug Discovery 10, 817-833 (Nov 2011)

Janus Initiative:
Quantified, Connected Stories to Develop Creative Consensus

Visually Compare Stakeholder Perspectives & Risk Assesment

Multiple outputs: Evidence & risk, financial, patient, health as viewed by each stakeholder



MAPPs/AL: 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

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New Pathways & New Sources of Evidence, what do we need?

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