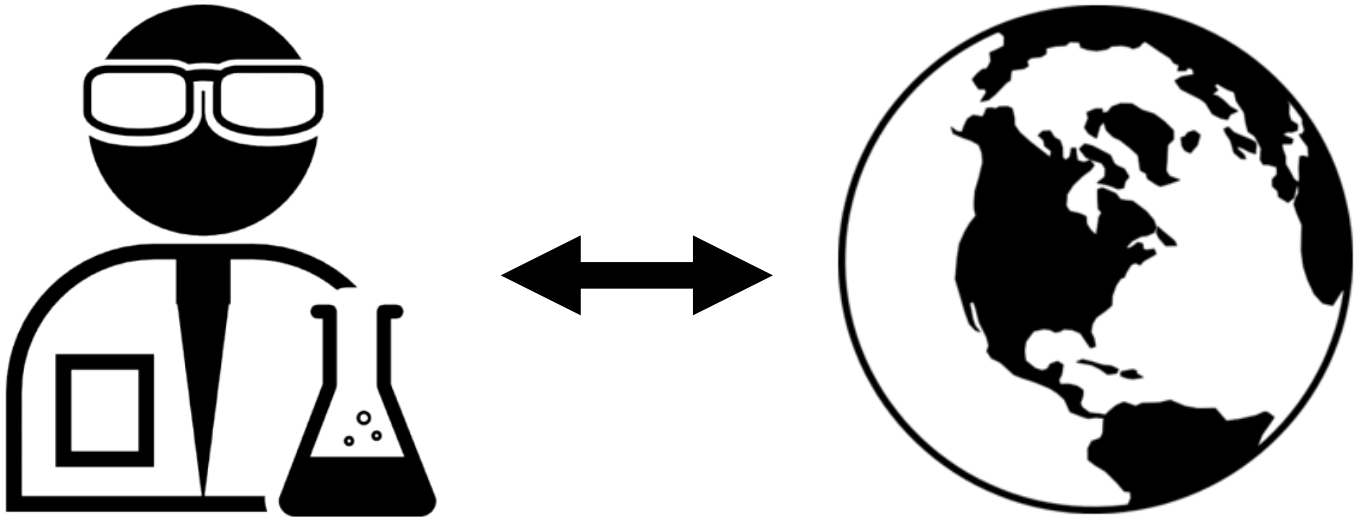


Real-World Evidence in Drug Development

M Vandemeulebroecke

Berlin, 18 Nov 2016

NOVARTIS

Agenda

1. Motivation
2. What is «real-world evidence»?
3. The «efficacy-effectiveness gap»
4. Real-world evidence in drug development
   a) Different studies, sources, questions
   b) Iterative approval and access
   c) New pricing / reimbursement schemes
5. Opportunities and Challenges
6. Conclusion

NOVARTIS

Agenda

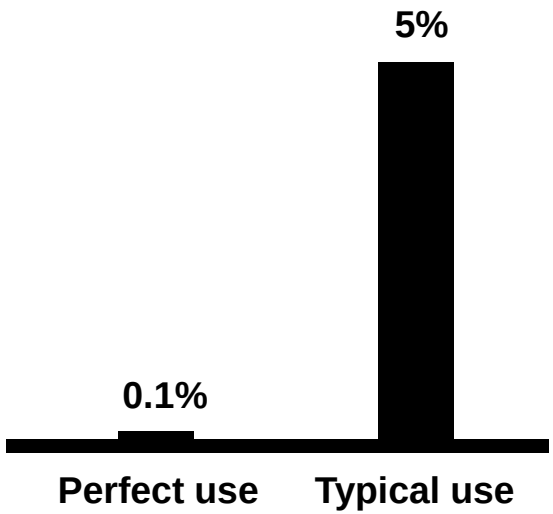
1. Motivation
2. What is «real-world evidence»?
3. The «efficacy-effectiveness gap»
4. Real-world evidence in drug development
   a) Different studies, sources, questions
   b) Iterative approval and access
   c) New pricing / reimbursement schemes
5. Opportunities and Challenges
6. Conclusion

NOVARTIS

Koop's law

Drugs don't work in patients who don't take them.

Example: Yearly conception rate with oral contraceptives



Centers for Disease Control and Prevention. Achievements in Public Health, 1900-1999 Family Planning. MMWR Morb. Mortal. Wkly, 1999

NOVARTIS

Agenda

1. Motivation
2. What is «real-world evidence»?
3. The «efficacy-effectiveness gap»
4. Real-world evidence in drug development
   a) Different studies, sources, questions
   b) Iterative approval and access
   c) New pricing / reimbursement schemes
5. Opportunities and Challenges
6. Conclusion

NOVARTIS

Perspectives on Drug Development

I need help*

Patient

I want to help*

Regulator

I want to help* – at an affordable level

Payer/HTA

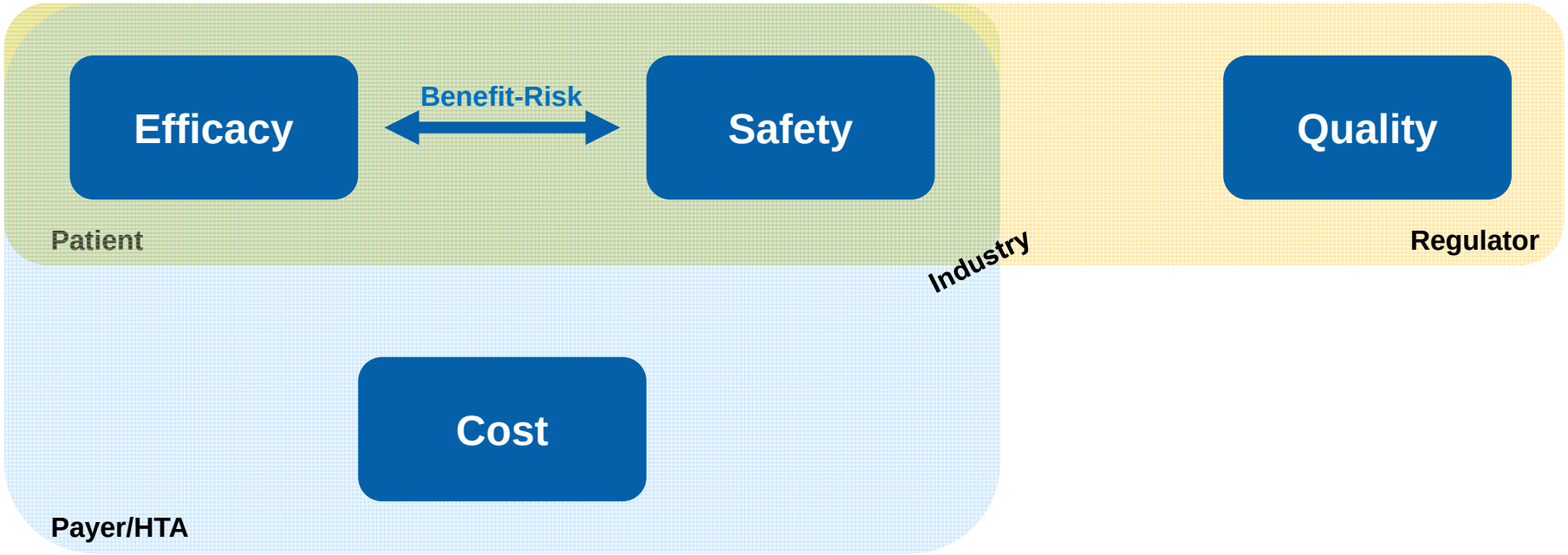
I want to help* – and make profit

Industry

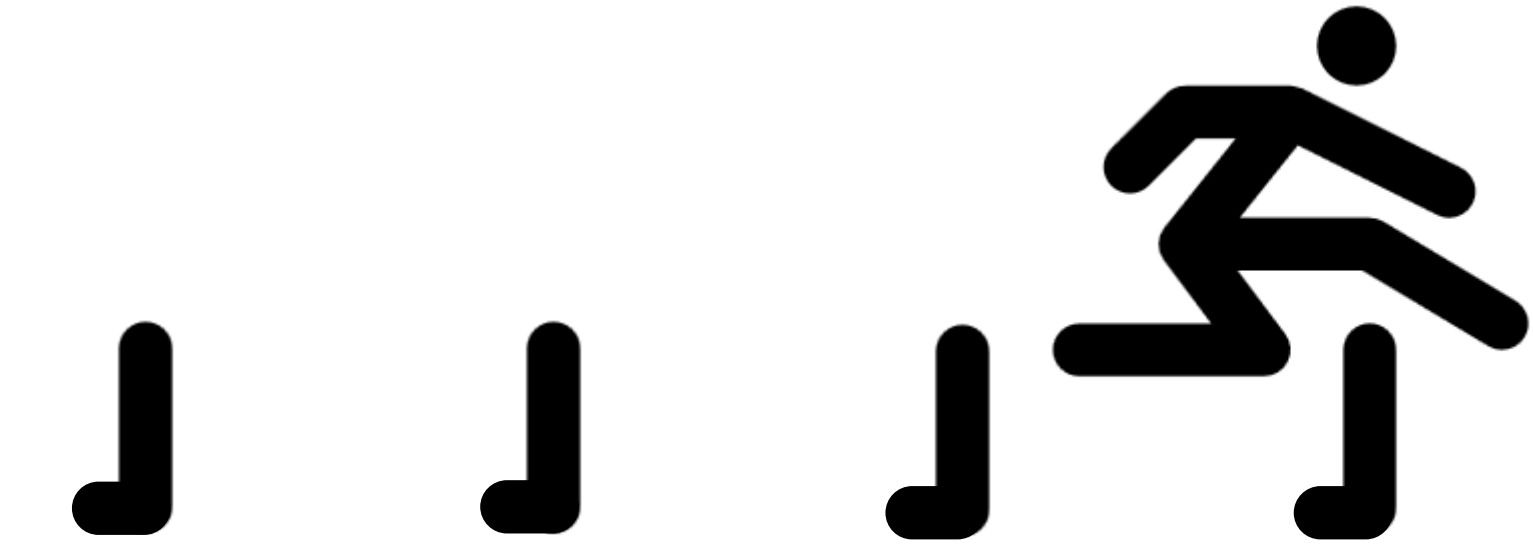
*...and no harm

NOVARTIS

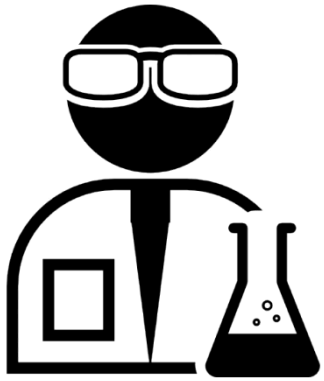
Major Drug Development Considerations (1)



The “four hurdles” to market



Efficacy vs. Effectiveness



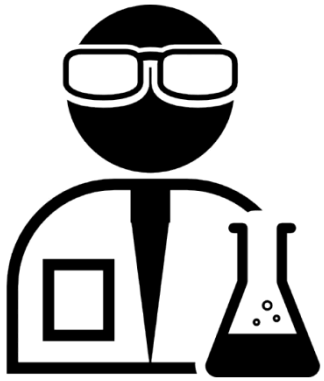
Efficacy can be defined as performance of a treatment under ideal and controlled circumstances

Effectiveness refers to the performance of a treatment under usual or '*real world*' circumstances

Revicki, Frank: *Pharmacoeconomic Evaluation in the Real World – Effectiveness vs Efficacy Studies*. Pharmacoeconomics 1999

NOVARTIS

Efficacy vs. Effectiveness



Efficacy is the extent to which an intervention does more good than harm under *ideal circumstances*

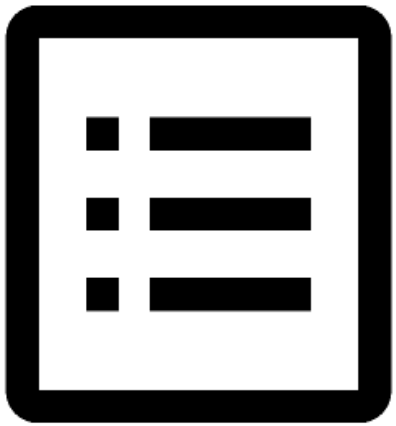
Effectiveness is the extent to which an intervention does more good than harm when provided under the *usual circumstances of health care practice*

Revicki, Frank: *Pharmacoeconomic Evaluation in the Real World – Effectiveness vs Efficacy Studies*. Pharmacoeconomics 1999

High Level Pharmaceutical Forum, http://ec.europa.eu/DocsRoom/documents/7581/attachments/1/translations/en/renditions/pdf

NOVARTIS

RWD and RWE



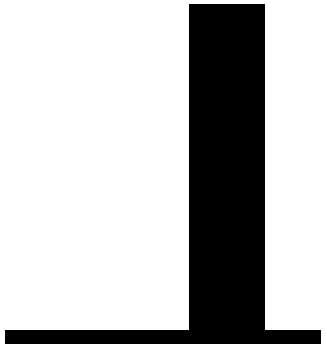
Real World Data (RWD) is an umbrella term for data regarding the effects of health interventions (e.g. benefit, risk, resource use, etc.) *that are not collected in the context of conventional randomised controlled trials*. Instead, RWD is collected both prospectively and retrospectively from observations of routine clinical practice. RWD can be obtained from many sources including patient registries, electronic medical records, and observational studies.

Real World Evidence (RWE) is the evidence derived from the analysis and/or synthesis of RWD.

Source: IMI-GetReal Glossary, WP1

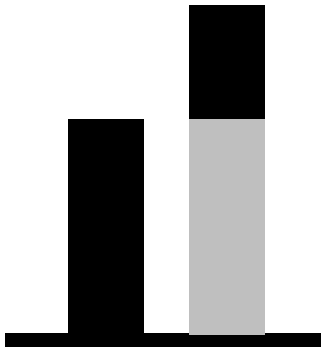
NOVARTIS

Absolute vs. Relative



Efficacy is the extent to which an intervention does more good than harm under ideal circumstances

Effectiveness is the extent to which an intervention does more good than harm when provided under the usual circumstances of health care practice



Relative efficacy can be defined as the extent to which an intervention does more good than harm, under ideal circumstances, *compared to one or more alternative interventions*

Relative effectiveness* can be defined as the extent to which an intervention does more good than harm *compared to one or more intervention alternatives for achieving the desired results* when provided under the usual circumstances of health care practice

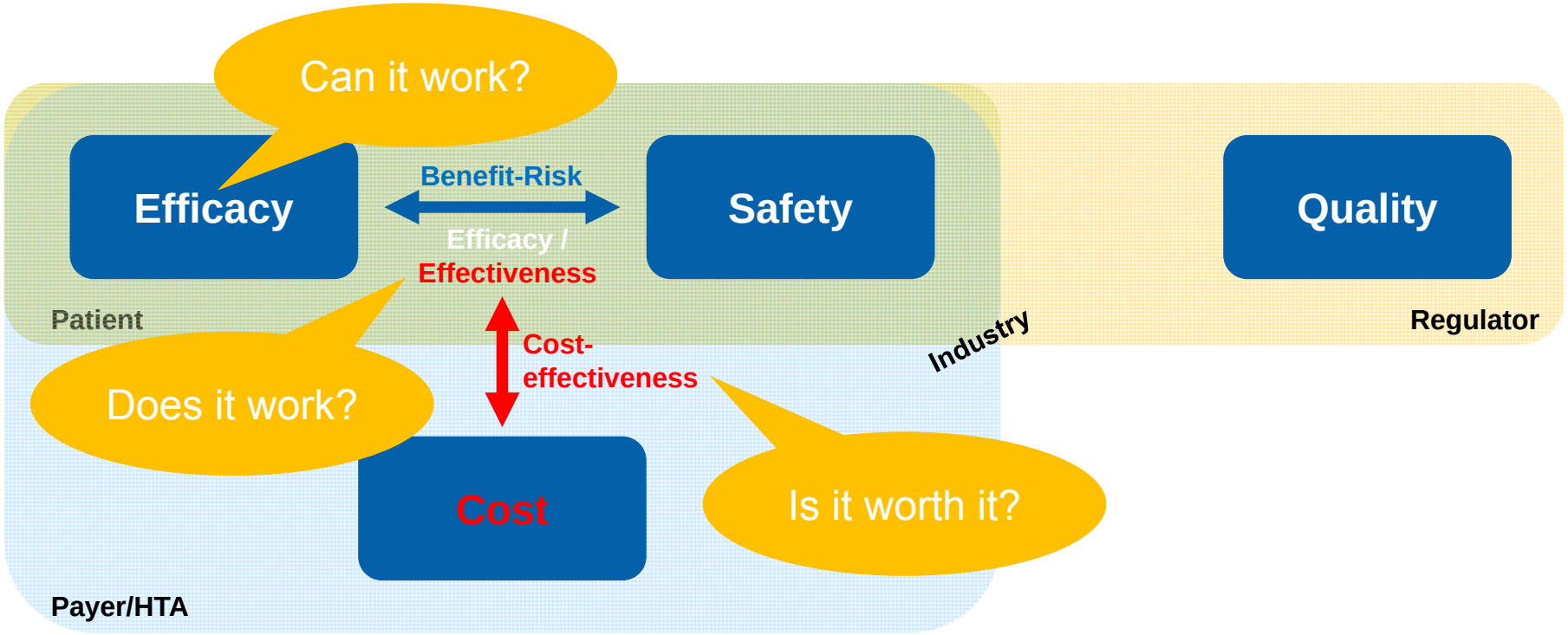
* *Comparative effectiveness (research)* in the US

Source: High Level Pharmaceutical Forum

NOVARTIS

Major Drug Development Considerations (2)

...with «real-world» elements in red font



NOVARTIS

Agenda

1. Motivation
2. What is «real-world evidence»?
3. The «efficacy-effectiveness gap»
4. Real-world evidence in drug development
   a) Different studies, sources, questions
   b) Iterative approval and access
   c) New pricing / reimbursement schemes
5. Opportunities and Challenges
6. Conclusion

NOVARTIS

Example: Rimonaband (Acomplia, Sanofi-Aventis) in EU

- Licenced for weight loss in 2006 (adjunct to diet and exercise)
  - Based on moderate effect with ≥ 1y treatment, outweighing low-incidence safety signals for depressive behavior
- Taken off market in 2009 due to reduced effect size and increased risks
  - Treatment duration often < 1y in real life
  - Prescribers often ignored warnings and contraindications in the label
  - Patients with comorbidity more susceptible to adverse mental effects

NOVARTIS

Example: Gefitinib (Iressa, AstraZeneca / Teva) in US

- Approved for non-small cell lung cancer (NSCLC) in 2003
  - Based on tumor response
  - Accelerated approval scheme
- Taken off market* in 2005 due to lack of effect on overall survival (OS)
- Approved again in 2015 for a subpopulation
  - Based on tumor response (follow-up for OS ongoing)
  - Mutation-positive epidermal growth factor receptor (EGFR)
  - With approved companion diagnostic
  - Orphan drug status

* except for patients already benefiting from the drug

NOVARTIS

Drivers of effectiveness

Health Care System
- Coverage / reimbursement
- Medical practices
- Screening policies

Biology
- Genomics
- Other intrinsic factors:
  - Demographics
  - Comorbidity
  - Disease stage / severity
- Extrinsic factors:
  - Environment (pollution, season, sunlight...)
  - Comedication
  - Food

Behavior
- Drug prescription
  - Off-label use
  - Co-prescribing with interacting drug
  - Dosing / medication errors
- Drug use
  - Adherence / persistence
  - Prior exposure
  - Over- / underdosing

Modified from Eichler et al.: *Bridging the efficacy-effectiveness gap: a regulator's perspective on addressing variability of drug response.* Nature reviews drug disc., 2011

NOVARTIS

Bridging the «efficacy-effectiveness gap»

- Let clinical trials reflect the real world?
  - Regulators to require demonstration of effectiveness?
  - Trials would be larger and more expensive
  - Signals may be lost in the noise: useful drugs may be missed
  - Demonstrating a drug's potential for delivering benefit is different from assessing whether that potential is achieved in real life
  - If there's a large efficacy-effectiveness gap after pivotal trials showed uncontroversial benefit, then this is not a drug problem but a health-care delivery problem
- Let the real world reflect clinical trials?
  - Identify the right patients for the drug
  - Enhance accurate prescription practice
  - Improve adherence

Eichler et al.: *Bridging the efficacy-effectiveness gap: a regulator's perspective on addressing variability of drug response.* Nature reviews drug disc., 2011

NOVARTIS

Agenda

1. Motivation
2. What is «real-world evidence»?
3. The «efficacy-effectiveness gap»
4. Real-world evidence in drug development
   a) Different studies, sources, questions
   b) Iterative approval and access
   c) New pricing / reimbursement schemes
5. Opportunities and Challenges
6. Conclusion

NOVARTIS

Example: Salford Lung Study (GSK)

Effectiveness of Fluticasone Furoate–Vilanterol for COPD in Clinical Practice

GUIDELINES ON THE MANAGEMENT OF chronic obstructive pulmonary disease (COPD) are based on numerous randomized, controlled trials of efficacy, which are usually generated for registration purposes.[1] However, these trials have included patients who were selected with the use of strict criteria and were closely monitored, and therefore the results have limited relevance to everyday clinical practice.[2] To counter this, it has been proposed that integrated comparative effectiveness trials involve more representative patients and be conducted in much less restricted environments.[3-5]

The Salford Lung Study was designed to evaluate the effectiveness and safety of the once-daily inhaled combination of fluticasone furoate and vilanterol (fluticasone furoate–vilanterol) as compared with existing maintenance therapy (usual care) in a large, real-world population of patients with COPD in conditions of normal care. The trial was initiated before the approval of fluticasone furoate–vilanterol in the United Kingdom and was conducted in and around Salford, United Kingdom, a community served mainly by a single hospital with an established electronic health record (EHR) system that connects primary and secondary care. This setting permits the unobtrusive observation of patients for effectiveness and safety monitoring, blended into routine clinical care.[6]

Vestbo et al., NEJM 2016

NOVARTIS

The many uses of RWE

a) Different studies, sources, questions

b) Iterative approval and access

c) New pricing / reimbursement schemes

- Prevalence, severity, subgroups
- Burden (humanistic / economic), unmet needs
- Patient journey, current treatment paradigms
- Comedications and comorbidities
- ...also locally!

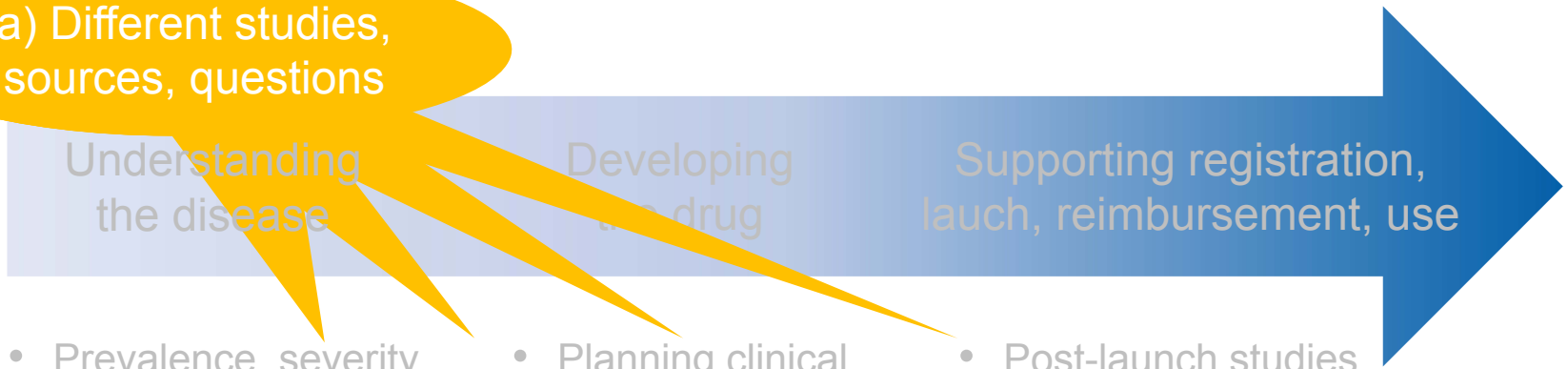
- Planning clinical trials (endpoints / outcomes, effect size, follow-up time, recruitment logistics)
- Understand competitors (effectiveness, use, safety, adherence, cost)
- Prepare launch, reimbursement, use (see right)

- Post-launch studies (outcomes / PRO
- Pricing / reimbursement (also outcome-based), resource use, cost-effectiveness
- Comparative effectiveness and safety (also indirect)
- Adherence, use patterns
- ...also locally!

NOVARTIS

The many uses of RWE

a) Different studies, sources, questions



- Prevalence, severity, subgroups
- Burden (humanistic / economic), unmet needs
- Patient journey, current treatment paradigms
- Comedications and comorbidities
- ...also locally!

- Planning clinical trials (endpoints / outcomes, effect size, follow-up time, recruitment logistics)
- Understand competitors (effectiveness, use, safety, adherence, cost)
- Prepare launch, reimbursement, use (see right)

- Post-launch studies (outcomes / PROs, safety, effectiveness, adherence); also observational, registries etc.
- Pricing / reimbursement (also outcome-based), resource use, cost-effectiveness
- Comparative effectiveness and safety (also indirect)
- Adherence, use patterns
- ...also locally!

NOVARTIS

Real-world studies

Real World Studies (RWS) are scientific studies investigating health interventions whose design does not follow the design of a randomised controlled clinical trial and aims to reflect health intervention effectiveness in routine clinical practice.

«They are low-quality evidence and full of biases.»

- ***Yes – when used to measure efficacy, but that's not their purpose. They are designed to NOT remove real-world drivers of effectiveness.***

«They could and should never replace randomized controlled trials.»

- ***Indeed – but again, they address a different question.***

«They are not generalizable.»

- ***Of course not! They depend on a given practice / healthcare system.***

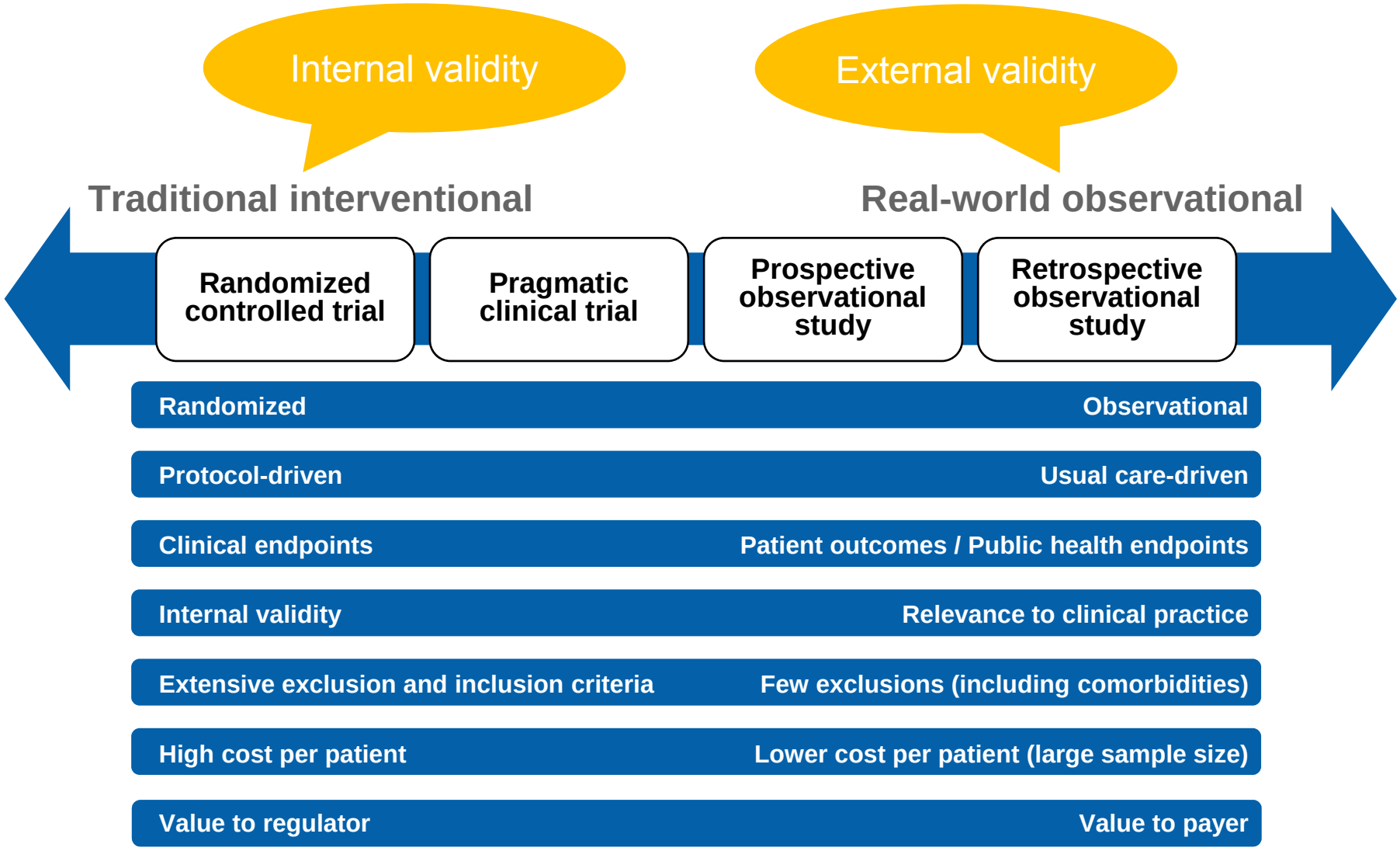
«They do not or cannot measure the right clinical endpoints.»

- ***Effectiveness outcomes are often different from clinical endpoints as they should have public health relevance.***

Sources: IMI-GetReal Glossary, WP1; Laser Analytica

NOVARTIS

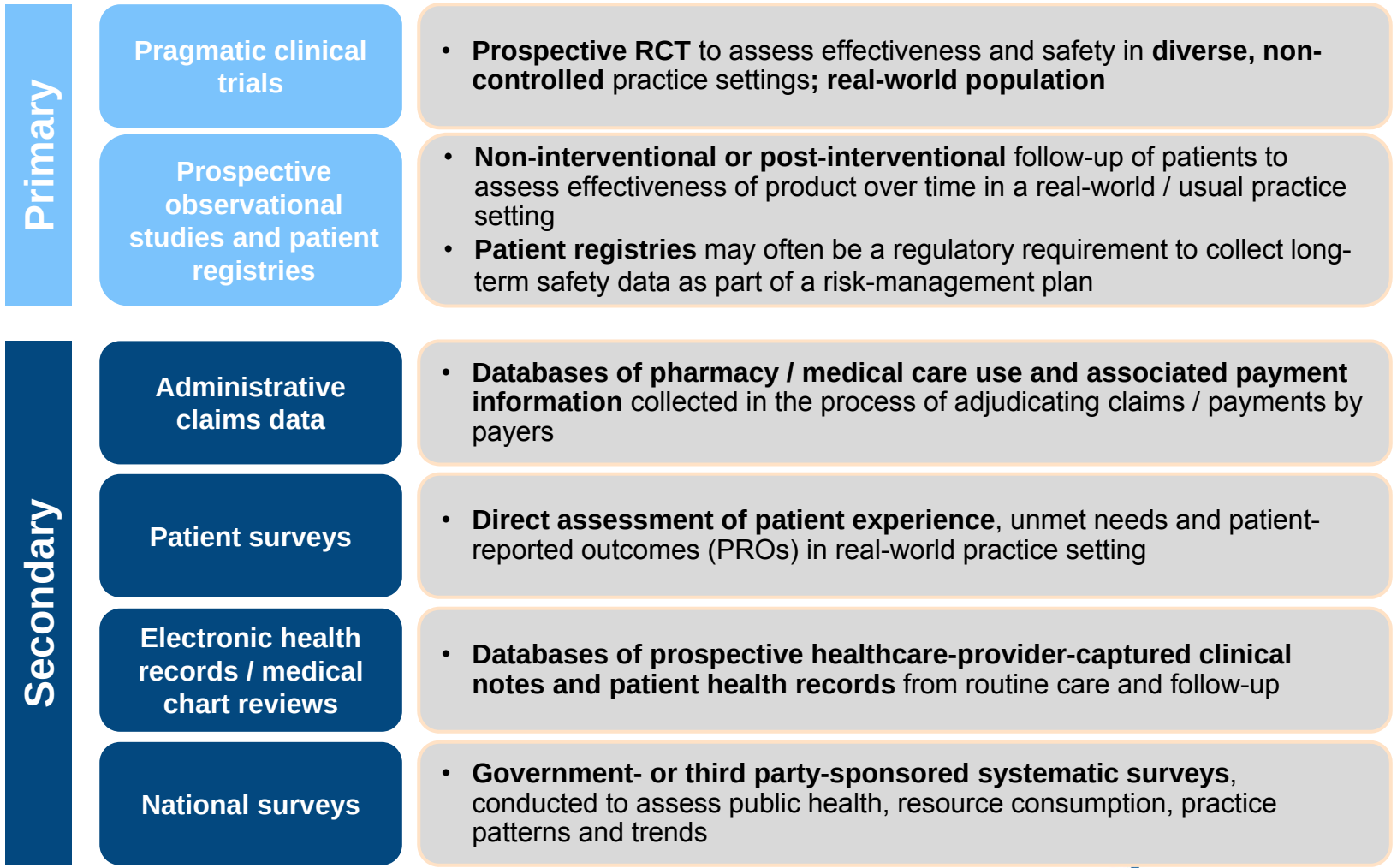
A spectrum of evidence



Modified from ISMPP 2015

NOVARTIS

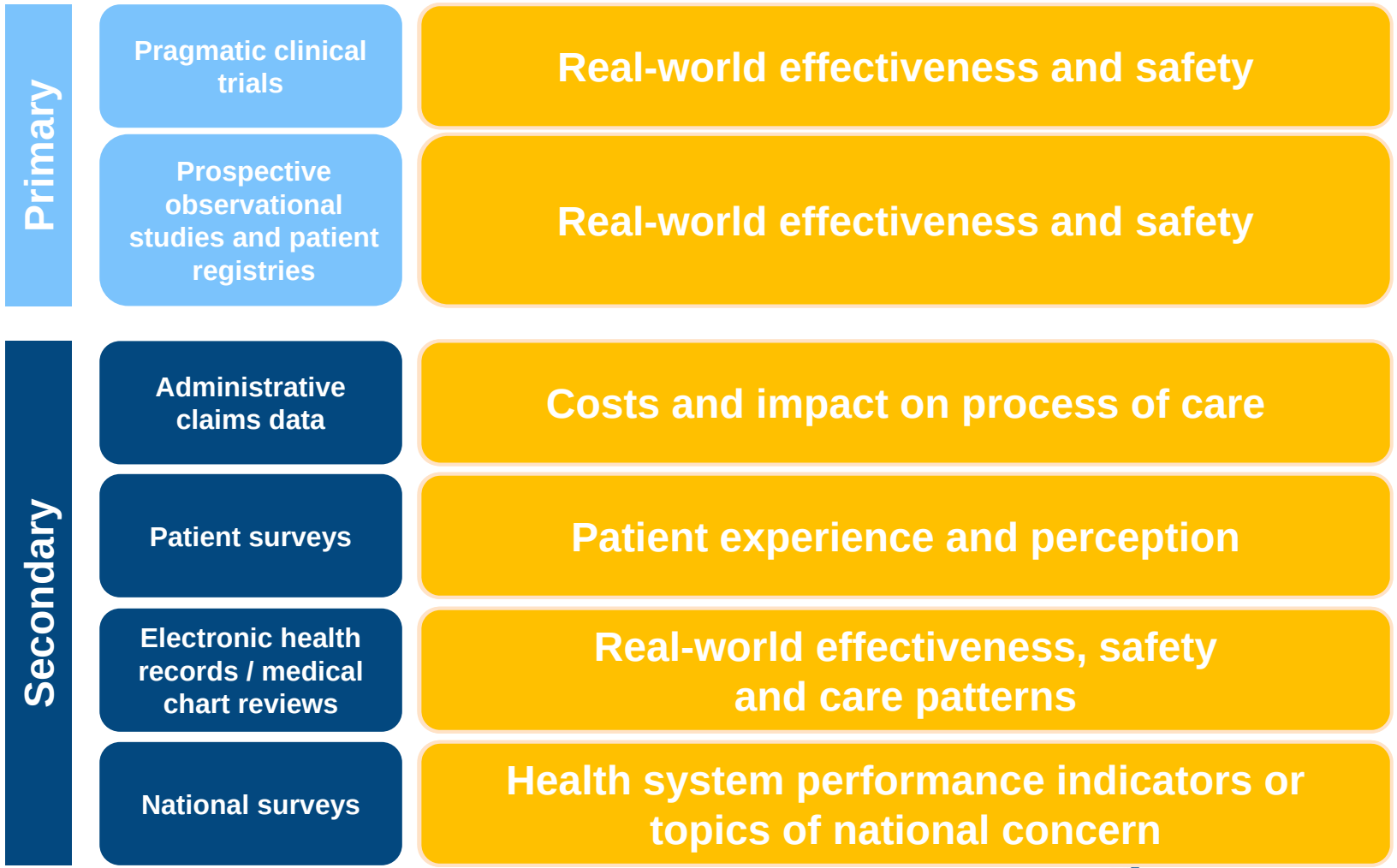
RWE sources and questions



Novartis Center of Excellence for RWE

NOVARTIS

RWE sources and questions



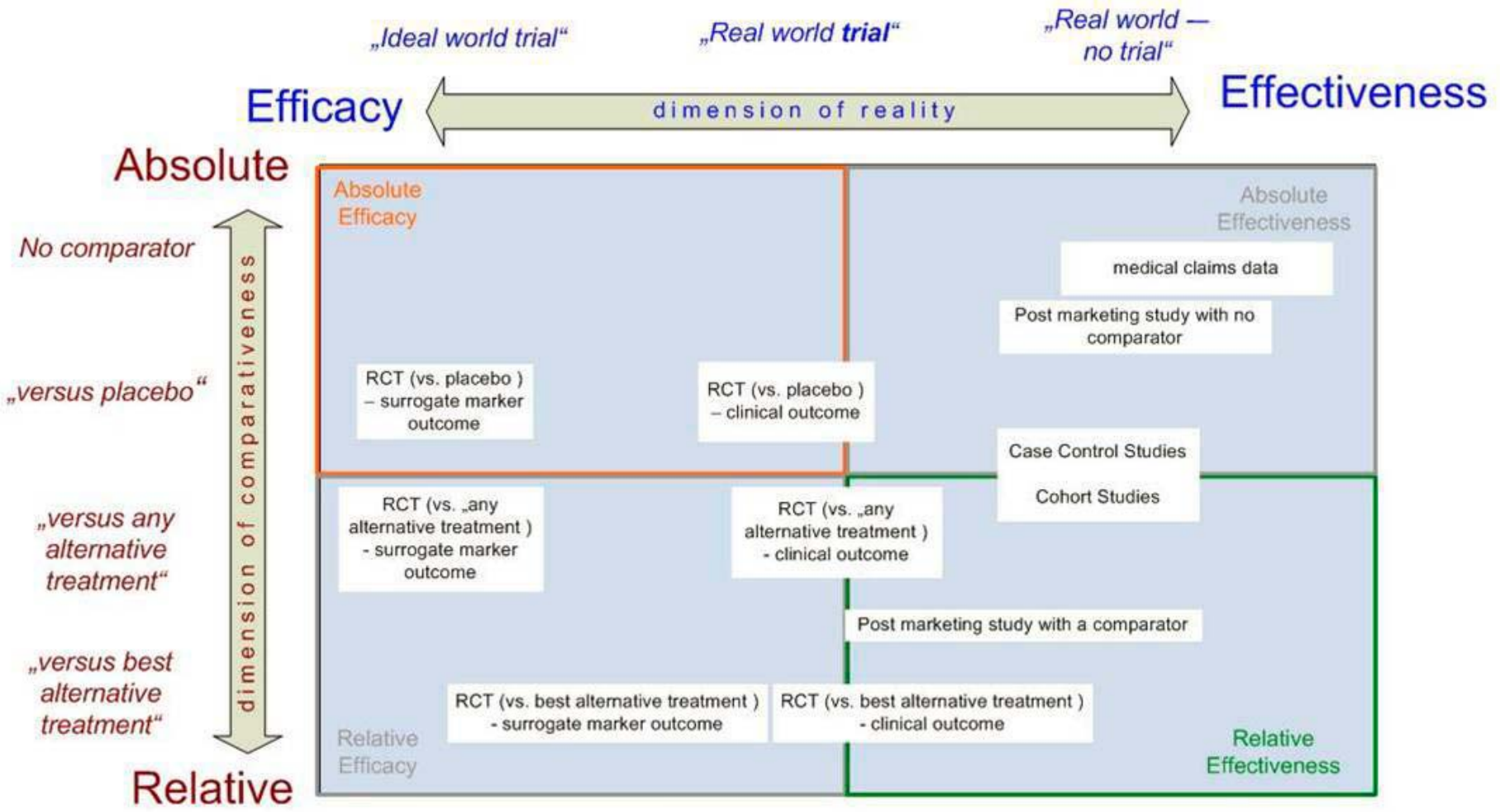
Novartis Center of Excellence for RWE

Some notes on RWE sources

- Primary sources: Typically good control over quality and fit-for-purpose
- Secondary sources: make the best of the available data
- Healthcare claims
  - PRO: Quite complete (care in all settings, low missingness, longitudinal follow-up), cost captured, large volume, readily available, cheap
  - CON: No clinical information, no disease onset, quality issues (e.g. misconduct), OTC drugs not well captured, availability time lag
- Medical records
  - PRO: Medical history, conmeds and clinical data available, cheap, near real-time availability
  - CON: No cost data, quality issues (e.g. lack of standardization, free text), loss to follow-up, focus on drug prescribing – not drug dispensing

NOVARTIS

Studies, sources, evidence



High Level Pharmaceutical Forum, http://ec.europa.eu/DocsRoom/documents/7582/attachments/1/translations/en/renditions/pdf

The many uses of RWE

b) Iterative approval and access

- Prevalence, severity, subgroups
- Burden (humanistic / economic), unmet needs
- Patient journey, current treatment paradigms
- Comedications and comorbidities
- ...also locally!

- Planning clinical trials (endpoints / outcomes, effect size, follow-up time, recruitment logistics)
- Understand competitors (effectiveness, use, safety, adherence, cost)
- Prepare launch, reimbursement, use (see right)

- Post-launch studies (outcomes / PROs, safety, effectiveness, adherence); also observational, registries etc.
- Pricing / reimbursement (also outcome-based), resource use, cost-effectiveness
- Comparative effectiveness and safety (also indirect)
- Adherence, use patterns
- ...also locally!

NOVARTIS

Approval and access: the «magic moment» or an iterative process?

PERSPECTIVES

See ARTICLE page 426

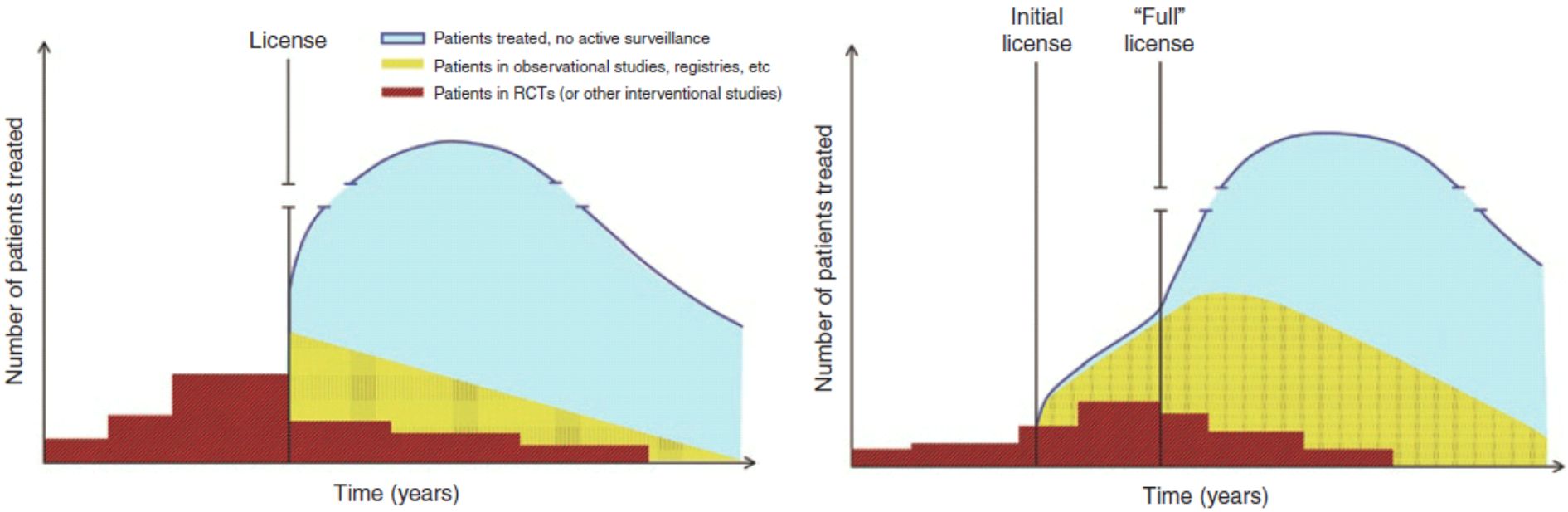
Evidence vs. Access: Can Twenty-First-Century Drug Regulation Refine the Tradeoffs?

J Woodcock[1]

As the pharmaceutical industry productivity crisis worsens, there are calls for regulatory changes to support innovation. At the same time, prescribers and payers desire more information about drugs at the time they are released to the market. Will new regulatory schemes be able to accommodate these disparate needs?

Woodcock, CPT 2012

EMA's adaptive licensing (2012)



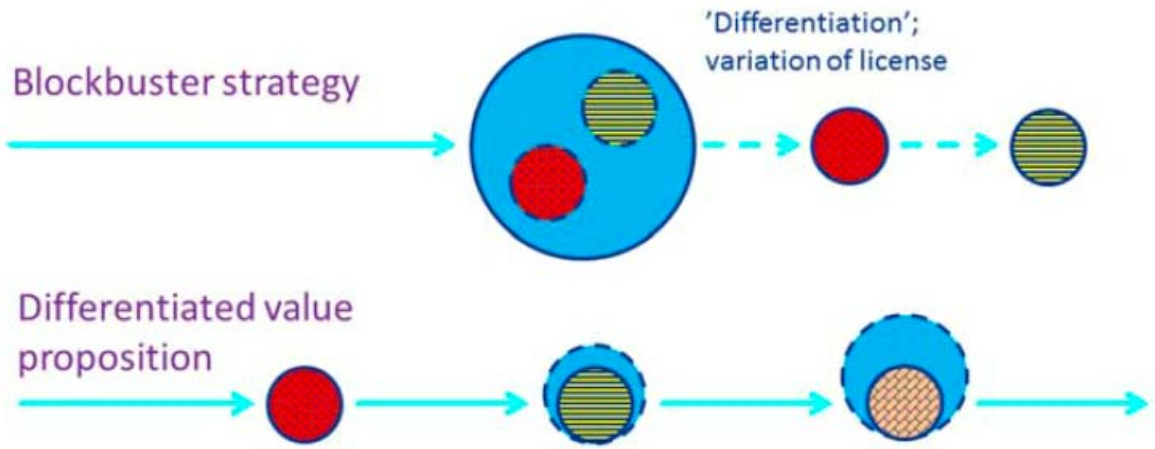
Standard licensing

Adaptive licensing

Eichler et al.: *Adaptive licensing: Taking the next step in the evolution of drug approval.* CPT 2012

EMA's adaptive pathways (2015)

- Medicines Adaptive Pathways to Patients (MAPP)
  - A prospectively planned, iterative approach to bringing medicines to market, encompassing development and data generation (incl. RWD)



  - Involvement of all relevant decision-makers across the life span of the medicine, including regulators and HTAs

Eichler et al.: *From adapt. licensing to adapt. pathways: Delivering a flexible life-span approach to bring new drugs to patients.* CPT 2015
Final report on the adaptive pathways pilot. *http://www.ema.europa.eu/docs/en_GB/document_library/Report/2016/08/WC500211526.pdf*

NOVARTIS

Other special development and approval schemes

Agency	Process	Condition	Advantages
FDA	Fast track designation (1988)	Unmet need in serious or life-threatening disease	Enhanced interaction and expedited review
	Accelerated approval (1992)	Serious or life-threatening disease	Approval possible based on surrogates (e.g. tumor regression)
	Priority review (1992)	Therapeutic advances	FDA action within 6 months
	Breakthrough therapy (2012)	Innovation & substantial improvement over existing therapies in serious disease (may be based on surrogates)	Accelerated approval process with scientific support
EMA	Accelerated assessment (2006)	Major public health interest, high unmet need	Assessment time reduced to 150 days
	Cond. marketing authorisation (2006)	Very serious and/or rare disease, high unmet need	Early approval based on less complete data
	Adaptive licensing (2012) / pathways (2015)	Scientific concept of iterative development and data generation incl. RWD, engagement with other healthcare decision makers	
	PRIME (2016)	Major public health interest, high unmet need	Dedicated support, accelerated assessment
PMDA	Regenerative medicines (2012)	Regenerative medicine (e.g. stem cell product)	Conditional, time-limited authorization based on safety and «probable efficacy»
	Sakigake strategy (2014)	Innovative product; serious or life-threatening disease	Earlier application, rapid authorization of unapproved / off-label drugs

Accelerated HTA processes

- 2014: UK's Office for Life Sciences (OLS) proposed "Early Access to Medicines" scheme for innovative drugs in rare diseases. Access would be granted after an initial MHRA assessment without NICE clearance.
- 2016: UK's NICE proposed a "lighter touch" process for treatments with estimated cost per QALY ≤ 10.000 £. Final NICE guidance would be issued immediately after marketing approval.

NOVARTIS

The many uses of RWE

- Prevalence, severity, subgroups
- Burden (humanistic / economic), unmet needs
- Patient journey, current treatment paradigms
- Comedications and comorbidities
- ...also locally!

- Planning clinical trials (endpoints / outcomes, effect size, follow-up time, recruitment logistics)
- Understand competitors (effectiveness, use, safety, adherence, cost)
- Prepare launch, reimbursement, use (see right)

- Post-launch studies (outcomes / PRO
effectiven
also obse
registries etc.
- Pricing / reimbursement (also outcome-based), resource use, cost-effectiveness
- Comparative effectiveness and safety (also indirect)
- Adherence, use patterns
- ...also locally!

c) New pricing / reimbursement schemes

NOVARTIS

Value-based pricing and new reimbursement schemes

Goal: increase efficiency in the health system

- Improve patient outcomes
- Reduce healthcare spending
- Reward innovation and effectiveness

NOVARTIS

Some quotes

- “We want to be rewarded for the tangible outcomes our products provide patients, not for simply selling pills.”
- “We must shift to a model that focuses on value and outcomes delivered, both to patients and to health systems.”
  - Meaningful outcomes
  - Patient experience
  - Benefit to the healthcare system
  - Societal value
- “Drug prices need to be backed by real-world data.”

J Jimenez, CEO Novartis, Forbes magazine, Nov 2016

NOVARTIS

Example: Rebif (Serono – Cigna)

From *Specialty Pharmacy News*

CIGNA Signs Outcomes-Based Contract That May Be First Deal for Specialty Drug

April 2011 Volume 8 Issue 4

Following the success of its first outcomes-based contract, one health plan recently signed a second such contract with a pharmaceutical manufacturer that may be the first to involve a specialty drug. CIGNA Corp.'s deal with EMD Serono, Inc. around the manufacturer's multiple sclerosis therapy Rebif (interferon beta-1a) is focused on helping prevent relapses in MS patients — adverse events that cost the health plan on average around $11,000 per hospitalization. Deals such as this are fairly rare at this point, but results from the initial contract, which was for diabetes management, are encouraging. And while experts predict more of these agreements, plans should keep in mind various factors that could hinder the success of such contracts.

CIGNA will track the percentage of hospitalization and emergency room visits avoided by people using Rebif by tracking medical claims in order to determine whether a relapse was the cause. The company will use 2010 as a baseline, looking at data from medical, pharmacy and lab claims, and measuring members' medication-possession ratio.

https://aishealth.com/archive/nspn0411-01

NOVARTIS

Outcomes-based risk-sharing agreements

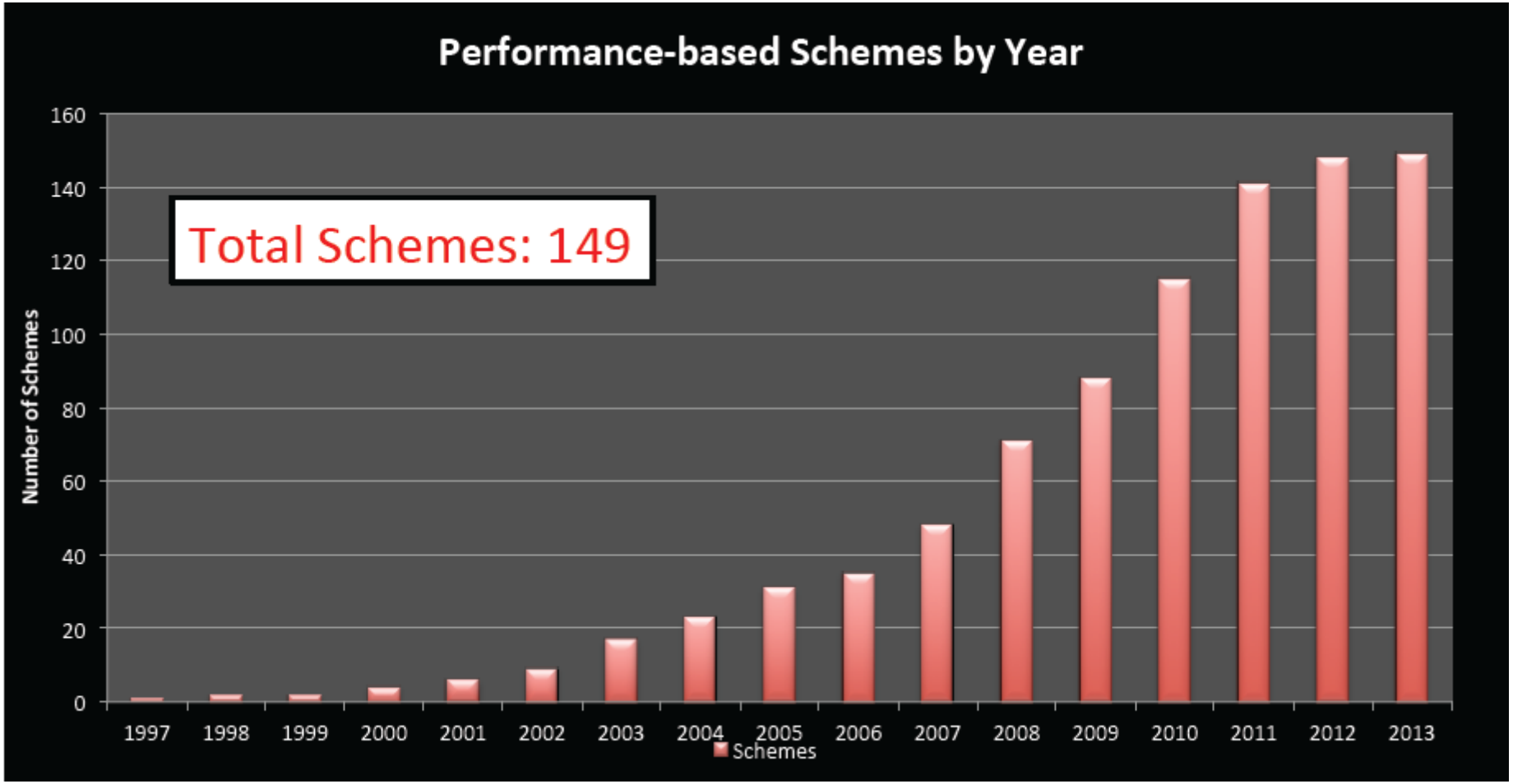
- Part of a proposed rule for a new Medicare payment model
  - Final price tied to actual outcomes rather than historic reference data
  - In the form of rebates, refunds, price adjustments etc.
- Variants / alternative names:
  - Performance-based pricing
  - Pay-for-performance (P4P)
  - Performance-linked reimbursement (PLR)
  - Coverage with evidence development (CED)
  - Conditional treatment continuation (CTC)
  - Patient access schemes (PAS)
  - ...

Medicare Program: Part B Drug Payment Model. https://www.regulations.gov/document?D=CMS-2016-0036-0002

J. Carlson, Univ of Washington. https://depts.washington.edu/pbrs/PBRS_slides.pdf

NOVARTIS

An increasing trend



J. Carlson, Univ of Washington

NOVARTIS

Agenda

1. Motivation
2. What is «real-world evidence»?
3. The «efficacy-effectiveness gap»
4. Real-world evidence in drug development
   a) Different studies, sources, questions
   b) Iterative approval and access
   c) New pricing / reimbursement schemes
5. Opportunities and Challenges
6. Conclusion

NOVARTIS

Opportunities

- Generate knowledge
  - Disease characteristics, health-care practice & economics, regional diff's
- Plan clinical trials
  - Endpoints and effect sizes of interest, study design, recruitment logistics
- Enable early access to promising drugs
  - By adopting an early approval scheme with subsequent RWE generation
- Support pricing/reimbursement
  - E.g. through outcome-based agreements, by region
- Demonstrate product value
  - Patient-centric, societal & economic, also regionally & vs. competitors
- Improve patient outcomes
  - E.g. by understanding and improving adherence or prescription

NOVARTIS

Challenges

- Statistical challenges
  - Dealing with biases (selection bias, publication bias, lack of blinding and randomization, missingness not at random, etc.)
  - Using large but unspecific databases, not-for-purpose secondary sources
  - Time trends
  - Combining evidence from clincial trials and real-world data
- Non-statistical challenges
  - Understanding the way the real-world data was generated (purpose / what's missing / biases?)
  - Creating good practice principles and technical infrastructures (common data models, dynamic database linking etc.)
  - Legal and privacy considerations
  - Interpreting possibly lower effectiveness than efficacy
  - Defend against (possibly flawed) real-world analyses from others
  - Transparency, validation, trust

NOVARTIS

Agenda

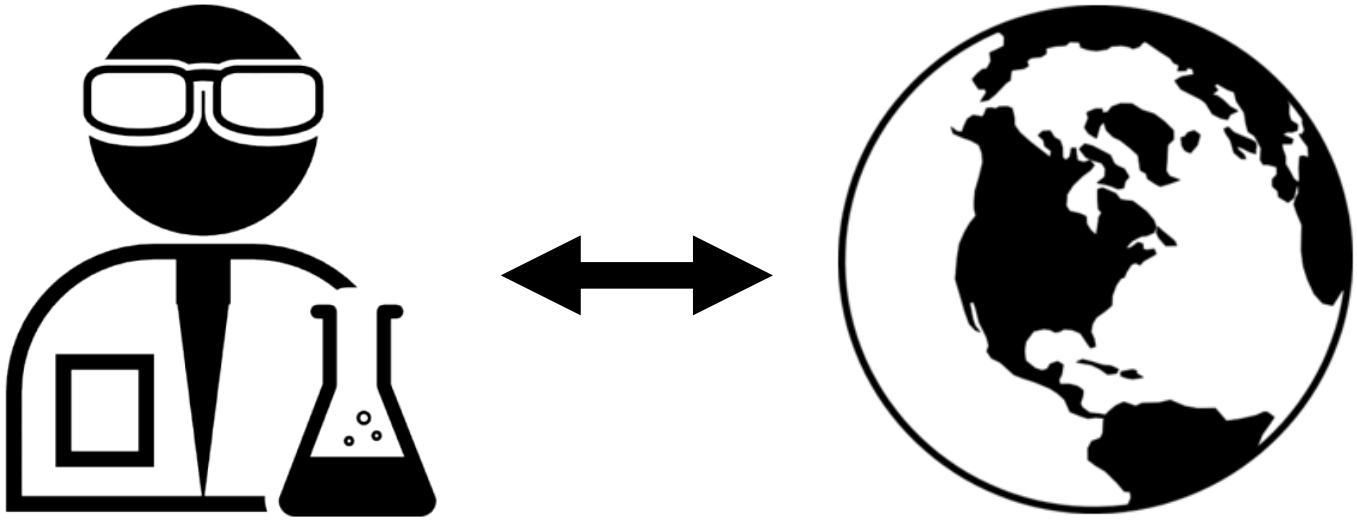
1. Motivation
2. What is «real-world evidence»?
3. The «efficacy-effectiveness gap»
4. Real-world evidence in drug development
   a) Different studies, sources, questions
   b) Iterative approval and access
   c) New pricing / reimbursement schemes
5. Opportunities and Challenges
6. Conclusion

NOVARTIS

Conclusion

- The role of RWD and RWE will continue to grow.
- RWD and RWE serve different purposes and adhere to different standards, compared to clinical trials.
- The optimal combination of both types of evidence is important for the success of drug development and commercialization.

NOVARTIS



Thank you

NOVARTIS

BACKUP

NOVARTIS

EBM and HTA

Evidence-based medicine (EBM) is the conscientious, explicit, and judicious use of current best evidence in making decisions about the care of individual patients.

Health technology assessment (HTA) is the systematic evaluation of properties, effects, and/or impacts of health care technology. It may address the direct, intended consequences of technologies as well as their indirect, unintended consequences. Its main purpose is to inform technology-related policymaking in health care. Health technology assessment is conducted by interdisciplinary groups using explicit analytical frameworks drawing from a variety of methods.

Sackett et al.: *Evidence based medicine: What it is and what it isn't*. BMJ 1996
International Network of Agencies for Health Technology Assessment (INAHTA).
Luce et al.: *EBM, HTA, and CER: clearing the confusion*. Milbank Quarterly 2010

EBM and HTA

Evidence-based medicine (EBM) is an evidence synthesis and decision process used to assist patients' and/or physicians' decisions. It considers evidence regarding the effectiveness of interventions and patients' values and is mainly concerned with individual patients' decisions, but is also useful for developing clinical guidelines as they pertain to individual patients.

Health technology assessment (HTA) is a method of evidence synthesis that considers evidence regarding clinical effectiveness, safety, cost-effectiveness and, when broadly applied, includes social, ethical, and legal aspects of the use of health technologies. The precise balance of these inputs depends on the purpose of each individual HTA. A major use of HTAs is in informing reimbursement and coverage decisions, in which case HTAs should include benefit-harm assessment and economic evaluation.

Sackett et al.: *Evidence based medicine: What it is and what it isn't*. BMJ 1996
International Network of Agencies for Health Technology Assessment (INAHTA).
Luce et al.: *EBM, HTA, and CER: clearing the confusion*. Milbank Quarterly 2010

EBM and HTA

Evidence-based medicine (EBM) is an evidence synthesis and decision process used to assist patients' and physicians' decisions. It considers evidence regarding effectiveness of interventions and patients' values and is primarily concerned with individual patients' decisions, but is also useful for developing clinical guidelines as they pertain to individual patients.

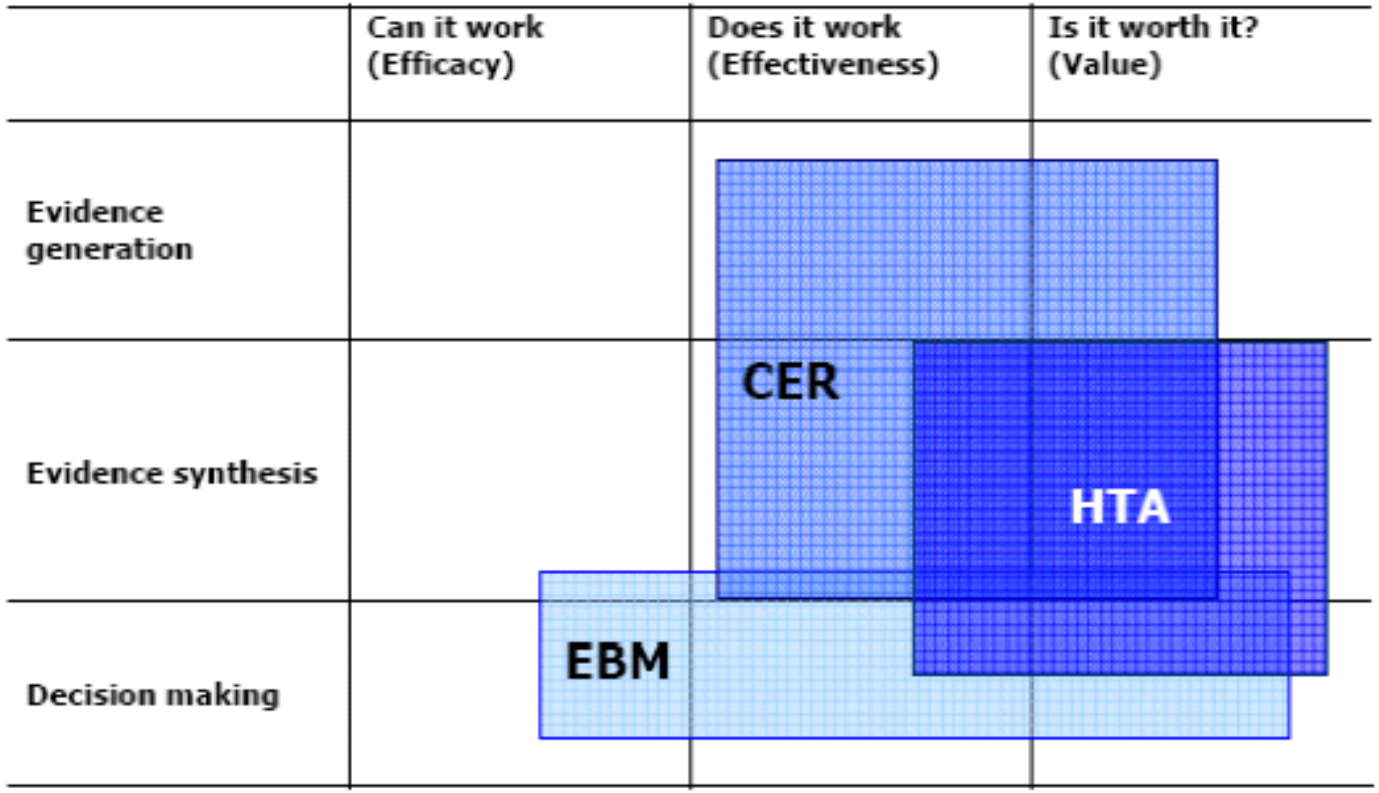
Focus on benefits to the patient

Health technology assessment (HTA) is a method of evidence synthesis that considers evidence regarding clinical effectiveness, safety, cost-effectiveness and, when broadly applied, includes social, ethical, and legal aspects of the use of health technologies. The precise balance of these inputs typically depends on the purpose of each individual HTA. A major use of HTAs is informing reimbursement and coverage decisions, in which case HTAs should include benefit-harm assessment and economic evaluation.

Focus on benefits to the society at large (often within budget constraints)

Sackett et al.: *Evidence based medicine: What it is and what it isn't*. BMJ 1996
International Network of Agencies for Health Technology Assessment (INAHTA).
Luce et al.: *EBM, HTA, and CER: clearing the confusion*. Milbank Quarterly 2010

EBM, CER and HTA



Luce et al.: *EBM, HTA, and CER: clearing the confusion*. Milbank Quarterly 2010